In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: March 29, 2024

KRISTEN COONS,	*	PUBLISHED
Petitioner,	*	No. 20-1067V
v.	*	Special Master Dorsey
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Tetanus Diphtheria Toxoid ("Td") Vaccine; Small Fiber Neuropathy.
Respondent.	*	

Andrew Donald Downing, Downing, Allison & Jorgenson, Phoenix, AZ, for Petitioner.
Joseph Adam Lewis, U.S. Department of Justice, Washington, DC, for Respondent.

RULING ON ENTITLEMENT[1]

On August 25, 2020, Kristen Coons ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program ("Vaccine Act" or "the Program"), 42 U.S.C. § 300aa-10 et seq. (2018),[2] alleging that she "developed a severe neurological injury" following a tetanus diphtheria toxoid ("Td") vaccination administered on June 23, 2019. Petition at Preamble (ECF No. 1). Respondent argued against compensation, stating "this case is not appropriate for compensation under the terms of the Vaccine Act." Respondent's Report ("Resp. Rept.") at 2 (ECF No. 19).

[1] Because this Ruling contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website and/or at https://www.govinfo.gov/app/collection/uscourts/national/cofc in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2018) (Federal Management and Promotion of Electronic Government Services). **This means the Ruling will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), Petitioner has 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material from public access.

[2] The National Vaccine Injury Compensation Program is set forth in Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 to -34 (2018) ("Vaccine Act" or "the Act"). All citations in this Ruling to individual sections of the Vaccine Act are to 42 U.S.C.A. § 300aa.

After carefully analyzing and weighing the evidence presented in accordance with the applicable legal standards, the undersigned finds Petitioner has provided preponderant evidence that her Td vaccine caused her neurological condition, small fiber neuropathy, satisfying Petitioner's burden of proof under Althen v. Secretary of Health & Human Services, 418 F.3d 1274, 1280 (Fed. Cir. 2005). Accordingly, Petitioner is entitled to compensation.

I. ISSUE TO BE DECIDED

Diagnosis is not at issue. The parties agree that Petitioner's diagnosis is small fiber neuropathy and that her symptoms persisted for longer than six months. Joint Submission, filed Apr. 27, 2023, at 1 (ECF No. 87). The parties dispute causation. The parties disagree as to whether Petitioner has established that her small fiber neuropathy was caused in fact by the Td vaccine she received on June 23, 2019.[3] See id.

II. BACKGROUND

A. Medical Terminology

Small fiber neuropathy is a "disorder of thinly myelinated and unmyelinated nerve fibers typically dominated by neuropathic pain and autonomic symptoms." Pet. Ex. 19 at 1.[4] Small fiber neuropathy "predominantly affects small-diameter peripheral nerve fibers, which include myelinated Aδ and unmyelinated C fibers" in the peripheral nervous system. Pet. Ex. 18 at 1.[5] Patients typically present with pain, tingling, numbness, burning, and coldness sensations in the lower extremities. Id.

The relatively common neuromuscular disorder can be associated with many medical conditions including diabetes mellitus, autoimmune diseases, vitamin B12 deficiency, viral infections, thyroid dysfunctions, sodium channelopathy, paraneoplastic syndrome, and others.

[3] Petitioner also received doses of the rabies vaccine on June 23, 2019, June 26, 2019, July 1, 2019, and July 8, 2019. Petitioner's Exhibit ("Pet. Ex.") 10 at 68, 173-74. The rabies vaccine is a non-covered vaccine on the Vaccine Injury Table and therefore, while it is sometimes discussed by the experts, the undersigned makes no findings regarding Petitioner's rabies vaccinations. See 42 C.F.R. § 100.3.

[4] C. Han et al., Na_v1.7-Related Small Fiber Neuropathy, 78 Neurology 1635 (2012).

[5] Lan Zhou, Small Fiber Neuropathy, 39 Seminars Neurology 570 (2019).

Pet. Ex. 18 at 1, 4-5. An autoimmune mechanism is often suspected in many patients with small fiber neuropathy. See Pet. Ex. 46;[6] Pet. Ex. 49;[7] Pet. Ex. 69.[8]

B. Procedural History

Petitioner filed her petition and medical records[9] on August 25 and 26, 2020. Petition; Pet. Exs. 1-9. Respondent filed his Rule 4(c) report, arguing against compensation, on May 19, 2021. Resp. Rept. at 2.

Petitioner filed an expert report from Dr. David Axelrod on July 9, 2021 and an expert report from Dr. Mitchell Gordon Miglis on August 17, 2021. Pet. Exs. 13, 43. Respondent filed an expert report from Dr. Thomas Leist on October 18, 2021. Resp. Ex. A. Petitioner filed a supplemental expert report from Dr. Axelrod on November 22, 2021 and a supplemental expert report from Dr. Miglis on December 27, 2021. Pet. Exs. 53-54. Respondent filed a supplemental expert report from Dr. Leist on February 11, 2022. Resp. Ex. L.

On April 12, 2022, the undersigned held a Rule 5 conference. Rule 5 Order dated Apr. 13, 2022 (ECF No. 53). The undersigned did not reach a preliminary finding as to causation. Id. at 2. The parties entertained settlement discussions from May 2022 to January 2023. See ECF Nos. 56, 72-79.

The parties subsequently agreed to resolve entitlement through a ruling on the record. Joint Status Rept., filed Feb. 27, 2023 (ECF No. 80). Petitioner filed her motion for a ruling on the record on April 27, 2023. Pet. Motion for Ruling on the Record ("Pet. Mot."), filed Apr. 27, 2023 (ECF No. 88). Respondent filed a response on July 5, 2023, and Petitioner filed a reply on August 1, 2023. Resp. Response to Pet. Mot. ("Resp. Response"), filed July 5, 2023 (ECF No. 93); Pet. Reply in Support of Pet. Mot. ("Pet. Reply"), filed Aug. 1, 2023 (ECF No. 94).

This matter is now ripe for adjudication.

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[6] Lorena M. Bitzi et al., Small Fiber Neuropathy: Swiss Cohort Characterization, 64 Muscle & Nerve 293 (2021).

[7] Jafar Kafaie et al., Small Fiber Neuropathy Following Vaccination, 18 J. Clinical Neuromuscular Disease 37 (2016).

[8] Vera Bril & Hans D. Katzberg, Acquired Immune Axonal Neuropathies, 20 Continuum 1261 (2014).

[9] Petitioner continued to file medical records throughout the course of litigation.

C. Factual History

1. Summary of Medical Records

Petitioner was born on February 3, 1983, and was 36 years old at the time of vaccination. Pet. Ex. 10 at 165. Petitioner's prior medical history consisted of depression and anxiety, vitamin B12 deficiency,[10] and occasional alcohol use. Id.

On June 20, 2019, three days prior to vaccination, Petitioner had a cognitive behavioral therapy session with Jennifer Heckler, M.S.W., L.C.S.W. Pet. Ex. 10 at 188. Petitioner reported that she was feeling drained from work. Id.

On June 23, 2019, Petitioner presented to an urgent care after being bitten by a dog on her nose the night before. Pet. Ex. 5 at 2. On physical examination, she denied extremity weakness, numbness in the extremities, and decreased mobility. Id. at 3. Her nose was red and swollen with several small lacerations/puncture wounds. Id. at 2, 4. The area was cleaned, and a triple antibiotic ointment (Bacitracin) was placed. Id. at 4. She was prescribed amoxicillin and instructed to go to the emergency department ("ED") if her symptoms worsened. Id. at 5.

Later that day, Petitioner presented to the ED for her dog bite injury as there was drainage coming from one of the puncture sites on her nose. Pet. Ex. 10 at 165. She had normal physical and neurological examinations. Id. at 166. Petitioner's culture from the drainage was positive for small gram-positive bacillus, gram-positive cocci, and she also had an elevated white blood cell count. Id. at 170-71. Her last tetanus shot was in 2013. Id. at 165; see Pet. Ex. 12 at 3. Therefore, Petitioner received the Td vaccine[11] and a rabies vaccine on June 23, 2019.[12] Pet. Ex. 10 at 166-69. The Td vaccine was administered intramuscularly in Petitioner's left thigh. Id. at 174. Petitioner also received antibiotics (Rocephin) in the ED and "her wound [was] irrigated with high pressure sterile saline" and "a little bit of the rabies immunoglobulin [was placed] in the [two] puncture sites of the intradermal areas of the nose." Id. at 166. She was discharged with instructions to apply antibiotic ointment twice daily and return if her symptoms worsened. Id. at 166-67.

On June 25, 2019, Petitioner followed up with nurse practitioner ("NP") Lucas Gruwell for her dog bite injury. Pet. Ex. 10 at 146. Physical examination was normal, and Petitioner denied any significant changes in pain. Id. at 147, 150. Petitioner was instructed to continue

[10] Petitioner was first diagnosed with vitamin B12 deficiency around 2014. Pet. Ex. 10 at 386. She had been prescribed monthly B12 supplement injections since at least 2015. Pet. Ex. 2 at 11.

[11] Petitioner received the Tenivac Td vaccine. Pet. Ex. 10 at 68.

[12] Petitioner received rabies immunoglobulin and the Imovax rabies vaccine on June 23, 2019. Pet. Ex. 10 at 68, 173-74. Petitioner received doses of the Rabavert rabies vaccine on June 26, July 1, and July 8, 2019. Id. at 68. Petitioner was informed she completed her 14-day rabies vaccination regimen on July 9, 2019. Id. at 92.

caring for the wound to her nose by taking antibiotics and applying the antibiotic ointment. Id. at 150. Petitioner did not report any leg pain or numbness. See id. at 146-50.

On June 28, 2019, Petitioner presented to Michael Jaorasdr, NP, with "[f]atigue, myalgia, [and] paresthesias." Pet. Ex. 10 at 114. Petitioner reported that she had been having fatigue for several months, "but leg pain and numbness x [two] days." Id. Petitioner described her fatigue as "sleeping a lot." Id. Petitioner was concerned about Lyme disease as her dog had previously tested positive for Lyme disease and they had traveled and camped outdoors. Id. at 114-15. It was noted Petitioner "did recently suffer from a dog bite to her nose and was treated with doxycycline which is [also] a treatment for Lyme disease," but that Petitioner still wanted to be tested for Lyme disease given her symptoms. Id. at 115. Review of systems was "[p]ositive for light-headedness, numbness or shooting pain in hands, arms, legs, or feet, excessive daytime sleepiness, headaches[,] and weakness in arms or legs." Id. at 117. Petitioner's dog bite wound was healing nicely and there were no signs of infection. Id. at 119. Nurse Jaorasdr noted that Petitioner's "fatigue and myalgias may be related to her anxiety and depression" which was also discussed. Id.

Petitioner returned to Nurse Jaorasdr on August 9, 2019 for left leg numbness. Pet. Ex. 10 at 64. Petitioner reported that "this started approximately [six] weeks ago after her [ED] visit" for treatment of a dog bite to her face. Id. It was noted that she "did get several vaccinations including rabies [in the] left thigh." Id. Petitioner reported that "since that time[,] she had numbness and decreased sensation in her left lower leg. [Petitioner] state[d] that she was not initially concerned, however, she state[d] that yesterday she had some difficulty walking and had an antalgic gait that favor[ed] her right side." Id. Review of systems was "[p]ositive for numbness or shooting pain in hands, arms, legs, or feet, excessive daytime sleepiness[,] [] weakness in arms or legs," and "feeling nervous, anxious, or on edge in past two weeks." Id. at 67. Petitioner's physical examination revealed "decreased sensation to her left lower leg." Id. at 68. The diagnosis was numbness lower extremity. Id. at 64, 68. Nurse Jaorasdr "discussed [Petitioner's] decreased sensation in her left leg possibly being from nerve damage secondary to vaccinations." Id. at 68. The plan was to follow up as needed. Id. at 69.

On August 23, 2019, Petitioner saw physiatrist Dr. Jerry Sobel for left leg numbness. Pet. Ex. 4 at 8. Petitioner reported that she was treated in the ED on June 23, 2019 for a dog bite when she received vaccinations in her left thigh. Id. "She noticed [two] days after the [ED] visit the numbness in the lateral aspect of her left leg." Id. "Her symptoms got progressively worse and she saw her primary care physician at the Mayo Clinic on August 9, 2019 because she was also experiencing a sense of weakness in the left leg." Id. She described the sense of weakness as "if she was sitting for a while and went to stand up it was like the left leg did not want to move and she shuffle[d] along and then it would start to feel better and she could walk normally." Id. She only had a few episodes of that. Id. Petitioner reported she felt she had "plateaued and [was] not getting any better." Id. There had been no testing or imaging done to date. Id. On examination, Petitioner had reduced sensation to her left leg. Id. "Manual muscle testing reveal[ed] normal strength except for the left great toe extensor at 4+/5." Id. And with dorsiflexion of her left foot, Petitioner had increased tingling in the lateral aspect of her left leg.

Id. at 9. "She had markedly positive Tinel's[13] over the peroneal nerve at the fibular head with shooting tingling into the lateral [left] leg." Id. Dr. Sobel's assessment was "a left L5 radiculopathy versus a peroneal nerve neuropathy at the fibular head," but "[i]t [was] [his] medical opinion that the latter [was] more likely especially as she is a habitual leg crosser preferring the left leg over the right." Id. Dr. Sobel ordered an electrodiagnostic evaluation. Id.

Petitioner followed up with Dr. Sobel on August 27, 2019. Pet. Ex. 4 at 2. An electromyography/nerve conduction study ("EMG/NCS") conducted that day showed decreased velocity in the left peroneal motor nerve, but there was no evidence of electrical instability in the examined muscles, and all remaining nerves were within normal limits. Id. Dr. Sobel noted there was "evidence for a mild left-sided peroneal nerve neuropathy at or around the fibular head involving motor fibers to both the [extensor digitorum brevis ("EDB") muscle][14] and tibialis anterior." Id. Petitioner was diagnosed with neuropathy of the left peroneal nerve and left leg numbness and weakness. Id. at 6.

On August 31, 2019, Petitioner sent a message to Nurse Jaorasdr stating that her EMG revealed myelin nerve damage as well as a blockage in her leg. Pet. Ex. 10 at 46. Petitioner wrote that the doctor

> mentioned that based on results and nerve location affected[,] he's ruled out back/spine issues and also said it's unlikely to be from the injection hitting a nerve (based on part of leg and nerve that is impacted). He mentioned it could be an autoimmune reaction from vaccination itself but that he didn't know enough about autoimmune diseases to say. [Petitioner was] reaching out to see if [Nurse Jaorasdr] [thought] vaccine-induced [Guillain-Barré syndrome ("GBS")][15] could be a concern?

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[13] A Tinel sign is "a tingling sensation in the distal end of a limb when percussion is made over the site of a divided nerve. It indicates a partial lesion or the beginning regeneration of the nerve." Tinel Sign, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=106510 (last visited Feb. 14, 2024).

[14] The EDB muscle is the "short extensor muscle of toes." Musculus Extensor Digitorum Brevis, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=90693 (last visited Mar. 19, 2024).

[15] GBS is a "rapidly progressive ascending motor neuron paralysis of unknown etiology, frequently seen after an enteric or respiratory infection. An autoimmune mechanism following viral infection has been postulated." Guillain-Barré Syndrome, Dorland's Med. Dictionary Online, https://www.dorlandsonline.com/dorland/definition?id=110689 (last visited Mar. 1, 2024). GBS "begins with paresthesias of the feet, followed by flaccid paralysis of the entire lower limbs, ascending to the trunk, upper limbs, and face; other characteristics include slight fever, bulbar palsy, absent or lessened tendon reflexes, and increased protein in the cerebrospinal fluid without a corresponding increase in cells." Id. Variant forms include acute autonomic neuropathy, acute motor axonal neuropathy, and acute motor-sensory axonal neuropathy. Id.

Id. Nurse Jaorasdr responded that the GBS question "would be for the provider who did the EMG testing." Id.

Petitioner saw orthopedist Dr. Cory Nelson on September 3, 2019 for left knee pain. Pet. Ex. 6 at 22. Petitioner reported that she started having numbness in her left leg, mainly from the knee down, two days after receiving a rabies vaccination in the ED. Id. She also reported foot weakness. Id. She denied any radicular pain and felt her main issue was numbness and weakness. Id. Examination of the left knee showed no swelling or effusion, normal strength, and normal range of motion. Id. at 23. "On palpitation, there [was] a positive Tinel's finding over the fibular neck/head." Id. Sensory examination of the left lower extremity showed diminished sensation in her left lower leg and "subtle" weakness of the left ankle with dorsiflexion. Id. There was also "some asymmetric diminished sensation at the lateral joint line and just proximal to the epicondyle, which would be proximal to the peroneal nerve." Id. Her gait was normal. Id. An X-ray of her left knee was normal. Id. at 23-24. The assessment was left knee joint pain, common left peroneal nerve compression, and lumbar disk herniation with radiculopathy. Id. at 24. Dr. Nelson noted that Petitioner's diminished sensation proximal to the left knee led him to believe the symptoms could be "more proximal than at the fibular head." Id. He recommended magnetic resonance imaging ("MRI") to rule out lumbar radiculopathy and nerve compression. Id. Petitioner was also prescribed a Medrol Dosepak. Id.

On September 6, 2019, Petitioner saw neurologist Dr. Pritish Pawar at Foothills Neurology for paresthesia and leg numbness. Pet. Ex. 7 at 2-3. History notes indicated Petitioner "was bitten by an unknown dog on her nose in June 2019. She received rabies and tetanus vaccination. Few days later, she started having numbness in distal left lower extremity. She had difficulty walking due to numbness in the left leg below the knee." Id. at 3. At the time of this visit, Petitioner reported the numbness in the distal left lower extremity persisted. Id. Review of symptoms was positive for "numbness/tingling and trouble sleeping." Id. She did not have numbness or tingling in any other extremities. Id. Petitioner denied weakness but reported "impaired temperature everywhere below shoulders." Id. at 3-4. It was noted that Petitioner's recent EMG/NCS "was interpreted as showing electrodiagnostic evidence for a mild left peroneal neuropathy at or around the fibular head involving motor fibers to both the EDB and tibialis anterior muscle." Id. at 3. The assessment was paresthesia and left common peroneal neuropathy at the fibular head. Id. at 4. MRIs of the brain and cervical spine were ordered as well as a repeat EMG/NCS. Id.

On September 13, 2019, Petitioner presented to neurologist Dr. David Saperstein at Center for Complex Neurology. Pet. Ex. 8 at 12. Notes indicated that two days after vaccination, Petitioner had "long sensation in her lower legs and the back of both thighs." Id. At the time of this visit, Petitioner was "still struggling with loss of sensation i[n] lower extremities and now it [was] present in her arms. At night she [] [had] burning in her hands." Id. Dr. Saperstein's assessment was that Petitioner had "sensory symptoms and multifocal distributions. This came on surely after tetanus and rabies injections. Possible that there was some immune response to these." Id. at 14. Dr. Saperstein questioned where the lesion was. Id. Repeat EMG/NCS done that day was normal with "no evidence of at least large fiber neuropathy." Id. Upon reviewing Petitioner's prior EMG/NCS, Dr. Saperstein opined the "incorrect placement of electrodes could have affected the calculation of conduction velocity." Id. Small fiber

neuropathy and a central nervous system process were diagnostic considerations. Id. It was noted that Petitioner had "diffuse abnormality of vibratory sensation. This would be expected given her normal nerve conduction findings. Also[,] she ha[d] absent reflexes. The same applie[d] to this. Perhaps she had injury from previous B12 deficiency. Alternatively, there may be a B12 deficiently presently." Id. The plan was to further evaluate small fiber neuropathy including a skin biopsy and lab tests. Id.

On November 8, 2019, Petitioner went to the ED for nausea and vomiting. Pet. Ex. 12 at 5. Td was listed as an allergy. Id. at 7-8. Petitioner was discharged that day. Id. at 12.

Petitioner followed up with Dr. Saperstein on November 14, 2019. Pet. Ex. 8 at 16. The skin biopsy from September 27, 2019 showed "[a]bnormal nerve fiber density at the distal site . . . consistent with a length-dependent neuropathy affecting the small nerve fibers." Id. at 39. Her lab results from September 13, 2019 were normal, including a normal level of vitamin B12 at 482 (normal range 232-1245 pg/mL).[16] Id. at 16, 34. Petitioner continued to have "persistent [burning]/tingling pain in various locations of bilateral extremities, with left worse than right." Id. at 16. The diagnosis was small fiber neuropathy. Id. at 17. Dr. Saperstein's wrote, "[g]iven the onset of symptoms in relation to the timing of receiving the rabies vaccine, this is likely the result of an autoimmune reaction to the vaccinations." Id. Dr. Saperstein explained that he "could not cure [Petitioner's] condition," but they could try treatments to reduce discomfort. Id. She was prescribed amitriptyline. Id.

On February 20, 2020, Dr. Saperstein followed-up with Petitioner. Pet. Ex. 8 at 20. It was noted that the amitriptyline was not tolerated and while she was prescribed Keppra in December, it was never filled. Id. The assessment at this visit was neuropathic pain and nonspecific symptoms in addition to small fiber neuropathy symptoms. Id. at 21. She was given a three-month trial of Keppra. Id.

Petitioner had a telehealth appointment with Dr. Saperstein on May 4, 2020 for follow-up of small fiber neuropathy. Pet. Ex. 8 at 28. She continued to have neuropathic pain. Id. at 29. She recently noticed similar symptoms in her abdomen. Id. at 28. "She had been unable to work due to pain and her symptoms were continuing to progress." Id. Petitioner had not yet started the Keppra due to concerns of side effects. Id. At this visit, Dr. Saperstein prescribed Petitioner gabapentin for her neuropathic pain. Id. at 29.

No other relevant medical records were filed.

2. Statement of Petitioner

Petitioner wrote a statement dated August 20, 2020. Pet. Ex. 1 at 4. Petitioner recalled that prior to June 23, 2019, she was healthy and only visited the doctor yearly for routine checkups. Pet. Ex. 1 at ¶ 13. She "always had good labs, [] never got seasonal cold/flu ([which] [she] chalked up to having a good immune system), rarely took medications (not even Tylenol)

[16] Petitioner's vitamin B12 level was previously low at 171 (normal range 180-914 ng/L) on July 31, 2018. Pet. Ex. 10 at 305, 428.

aside from a [B]12 vitamin, had a healthy vegetarian diet, and was physically active." Id. Importantly, prior to receiving the Td vaccine on June 23, 2019, Petitioner "had no issues with neuropathy or weakness in [her] lower extremities." Id. at ¶ 2.

On June 22, 2019, Petitioner was bit on the nose by a dog. Pet. Ex. 1 at ¶ 3. Petitioner stated that the injury became infected and the next day, June 23, 2019, she went to get it checked out at an urgent care. Id. At that time, Petitioner was mostly concerned about scarring. Id. The urgent care told her they were unable to close the wound given the amount of time since the dog bite occurred and instructed her to go to the hospital. Id. Petitioner then went to the ED where they told her that "due to bacteria[,] they couldn't close it and administered a tetanus and rabies vaccination." Id.

On June 25, 2019, Petitioner recalled that her "leg kept losing feeling," explaining "it was almost like when you lay on one side too long and it goes to 'sleep' but instead of feeling coming back[,] [she] just couldn't feel it at all." Pet. Ex. 1 at ¶ 4. This had never happened to her before, and by June 28, she noticed her symptoms were getting worse. Id. at ¶ 5. By August of 2019, Petitioner "could no longer walk without losing balance." Id. at ¶ 6. And "[e]ven sitting down, [she] couldn't feel anything. Id.

In September 2019, Petitioner had absent reflexes and was "diagnosed with small fiber neuropathy damage caused by vaccination." Pet. Ex. 1 at ¶ 7. "[She] couldn't feel [her] arms or any vibrations when tested." Id. Petitioner reported "losing all [her] hair and look[ing] like a cancer patient." Id. She was unable to do any of her normal activities. Id. Petitioner reported having "to go on short-term disability from work because [she] couldn't even sit for extended periods." Id. She described that when she lied down to go to sleep, all she felt was what she imagined "lava going through veins [would] feel like." Id. Petitioner further explained "[i]t burn[t] and [her] extremities [felt] like how you feel when you are in snow and your hands get so cold then you put them under hot water." Id.

By November 2019, Petitioner "still felt horrible." Pet. Ex. 1 at ¶ 9. While Petitioner did not report losing any weight, "the elasticity of [her] facial skin seem[ed] to be deteriorating. It's like [she] aged overnight." Id. Petitioner "ke[pt] getting sick and throwing up" and recalled it was "like the muscles [weren't] working and [she was] choking on [her] own vomit." Id. Additionally, she wrote the muscles in her legs had atrophied and looked "like they [were] wasting away." Id.

In January 2020, Petitioner still felt "weak" and now she described "pressure on [her] eyes like they [were] going to bulge out of [her] head." Pet. Ex. 1 at ¶ 10. She also recalled painful urination and kept getting referred to neurology and "told it's all part of this injury." Id. By February 2020, Petitioner stated she developed cellulitis and had open wounds on her feet. Id. at ¶ 11.

Lastly, Petitioner wrote that when this first all started, her initial thought was that her condition resulted from the rabies vaccine, so that is what she told her doctors. Pet. Ex. 1 at ¶ 14. She "figured the rabies vaccine is such a unique and rare thing to get, that that must have been what caused all this. [She] figured it couldn't possibly be a vaccine that people get normally

(like the tetanus vaccine)." Id. Petitioner said she "had no idea that the tetanus vaccine [was] capable of causing neurological injury like small fiber neuropathy." Id.

3. Statement of Dr. Saperstein

Dr. Saperstein authored a statement on March 6, 2023. Pet. Ex. 57 at 1. Dr. Saperstein was Petitioner's treating neurologist in 2019. Id. He wrote that Petitioner received tetanus and rabies vaccinations because of a dog bite. Id.

Dr. Saperstein determined that Petitioner developed symptoms of small fiber neuropathy two days after receiving the vaccinations and "that it was likely the result of an autoimmune reaction to a vaccination." Pet. Ex. 57 at 1. He did not take any steps "to determine which vaccination would have caused the autoimmune reaction and [did] not have an opinion as to whether the autoimmune reaction and resulting small fiber neuropathy was caused by the tetanus or the rabies vaccination." Id.

D. Expert Reports

1. Petitioner's Expert, Dr. David Axelrod[17]

a. Background and Qualifications

Dr. Axelrod is a clinical immunologist board-certified in internal medicine, adult rheumatology, and allergy and immunology. Pet. Ex. 13 at 1. He received his M.D. at the University of Michigan Medical School, and his master's degree in Clinical Research Design and Statistical Analysis at the University of Michigan School of Public Health. Id. Dr. Axelrod completed a fellowship in allergy, immunology, and rheumatology at McGill University and was a medical staff fellow in the clinical immunology laboratory at the National Institutes of Health ("NIH"). Pet. Ex. 82 at 1. Dr. Axelrod has authored or co-authored several publications. Id. at 3-4. He is currently retired from patient healthcare but as a clinician he was "involved with the diagnosis and treatment of individuals with drugs reactions (including to vaccines)." Pet. Ex. 13 at 1.

b. Opinion

Dr. Axelrod opined Petitioner had a "secondary adaptive immune response" to the components of the Td vaccine which also reacted to "similar and/or homologous amino acid sequences of [Petitioner's] cutaneous small fiber neurons, resulting in stimulation and/or damage to her cutaneous small fiber neurons." Pet. Ex. 13 at 14. According to Dr. Axelrod, Petitioner "developed a protective immune response to the Td booster, which also activated self-reactive immune cells to produce an immune response to her small peripheral nerve fibers with damage" resulting in small fiber neuropathy three days after her vaccination. Pet. Ex. 53 at 8.

[17] Petitioner filed two expert reports from Dr. Axelrod. Pet. Exs. 13, 53.

i. Althen Prong One

The mechanistic theory proposed by Dr. Axelrod for how the Td vaccine can cause small fiber neuropathy was molecular mimicry. Pet. Ex. 13 at 6. Dr. Axelrod provided a general overview of the role of molecular mimicry in autoimmune diseases with supportive literature. Id. at 6-7 (citing Pet. Ex. 27;[18] Pet. Ex. 28;[19] Pet. Ex. 29;[20] Pet. Ex. 30;[21] Pet. Ex. 31;[22] Pet. Ex. 61).[23] Molecular mimicry occurs "when similarities between foreign and self-peptides favor an activation of autoreactive T or B cells by foreign-derived peptides in a susceptible individual." Id. at 6 (quoting Pet. Ex. 61 at 1); see also Pet. Ex. 63 (describing molecular mimicry in autoimmune disease).[24] "T cell activation of CD8+ and CD4+ T cells results from the recognition of antigenic peptides in the context of self MHC class I or class II molecules respectively." Pet. Ex. 35 at 1;[25] see also Pet. Ex. 32 (describing the adaptive immune response).[26]

Dr. Axelrod proposed that molecular mimicry can cause small fiber neuropathy by directing an "immune response to the elements involved in the development of inflammatory disease of the small sensory unmyelinated type C-fibers and in the myelinated type Aδ fibers of the small sensory fibers of the skin." Pet. Ex. 13 at 6. Dr. Axelrod opined that there is homology between amino acid sequences of the components of the Td vaccine and various small

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[18] Jean-Marie Fourneau et al., The Elusive Case for a Role of Mimicry in Autoimmune Diseases, 40 Molecular Immunity 1095 (2004).

[19] Darja Kanduc et al., Massive Peptide Sharing Between Viral and Human Proteomes, 29 Peptides 1755 (2008).

[20] Brett Trost et al., Bacterial Peptides Are Intensively Present Throughout the Human Proteome, 1 Self/Nonself 71 (2010).

[21] Matthew F. Cusick et al., Molecular Mimicry as a Mechanism of Autoimmune Disease, 42 Clinical Rev. Allergy & Immunology 102 (2012).

[22] Gerhild Wildner & Maria Diedrichs-Möhring, Molecular Mimicry and Uveitis, 11 Frontiers Immunology 580636 (2020).

[23] Manuel Rojas et al., Molecular Mimicry and Autoimmunity, 95 J. Autoimmunity 100 (2018).

[24] Noel R. Rose, Negative Selection, Epitope Mimicry and Autoimmunity, 49 Current Op. Immunology 51 (2017).

[25] Bernhard Hemmer et al., Minimal Peptide Length Requirements for CD4 + T Cell Clones—Implications for Molecular Mimicry and T Cell Survival, 12 Int'l Immunology 375 (2000).

[26] Abdul K. Abbas et al., Properties and Overview of Immune Responses, in Cellular and Molecular Immunology 1 (9th ed. 2018).

fiber nerve receptors. Id. at 9. First, the Tenivac vaccine contains a tetanus toxoid and a diphtheria toxoid. Id. at 7.

Second, immune-mediated small fiber neuropathy has been found to be related to sodium and potassium channels and nicotinic-ganglionic receptors. Pet. Ex. 21 at 10-12;[27] Pet. Ex. 22 at 2 tbl.1.[28] Specifically, peptides relevant to small fiber neuropathy include Transient Receptor Potential Vanilloid 1 ("TRPV1") in small sensory type C-fibers and in type Aδ fibers; sodium channel mutations such as NaV1.7, NaV1.8, and NaV1.9; Dorsal Root Ganglion Alpha-7 nicotinic receptor; and voltage-gated potassium channels such as Contactin-associated protein-like 2 ("CASPR2"). Pet. Ex. 13 at 8 (citing Pet. Ex. 21 at 10-12 (identifying sodium channels and CASPR2 in patients with small fiber neuropathy); Pet. Ex. 19 (identifying sodium channels as being expressed in small fiber neuropathy); Pet. Ex. 24 at 6-7 (stating the Doral Root Ganglion Alpha-7 nicotinic acetylcholine receptor is present in human dorsal root ganglions);[29] Pet. Ex. 25 at 2 (stating the TRPV1 channels "are predominantly expressed in small sensory C-fiber nerves and . . . Aδ fibers");[30] Pet. Ex. 26 at 8 (same);[31] Pet. Ex. 22 at 2 tbl.1; (associating immune-mediated small fiber neuropathy with potassium channel and nicotinic-ganglionic receptor antibodies)). Dr. Axelrod explained that these peptides "form parts of the unmyelinated type C fibers and myelinated type Aδ fibers" that are stimulated and/or damaged in small fiber neuropathy. Id. at 9.

Next, Dr. Axelrod conducted an Align search on UniProtKB[32] to determine whether there was any similarity, or sequence homology, between the components of the Tenivac Td vaccine and the relevant peptides in small fiber neuropathy. Pet. Ex. 13 at 8-9; see Pet. Exs. 14-15

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[27] Christopher H. Gibbons, Small Fiber Neuropathies, 20 Continuum 1398 (2014).

[28] Todd D. Levine, Small Fiber Neuropathy: Disease Classification Beyond Pain and Burning, 10 J. Central Nervous Sys. Disease (2018). This is also cited as Pet. Ex. 45.

[29] Xiulin Zhang et al., Nicotine Evoked Currents in Human Primary Sensory Neurons, 20 J. Pain 810 (2019).

[30] Michael R. Brandt et al., TRPV1 Antagonists and Chronic Pain: Beyond Thermal Perception, 5 Pharmaceuticals 114 (2012).

[31] A. Guo et al., Immunocytochemical Localization of the Vanilloid Receptor 1 (VR1): Relationship to Neuropeptides, the $P2X_3$ Purinoceptor and IB4 Binding Sites, 11 Eur. J. Neuroscience 946 (1999).

[32] UniProt is the Universal Protein Resource—"a comprehensive resource for protein sequence and annotation data." About UniProt, UniProt, https://www.uniprot.org/help/about (last visited Mar. 1, 2024). UniProtKB is the UniProt Knowledgebase. UniProtKB, UniProt, https://www.uniprot.org/help/uniprotkb (last visited Mar. 1, 2024). The Align function allows users to "align two or more protein sequences . . . to view their characteristics alongside each other." Sequence Alignments, UniProt, https://www.uniprot.org/help/sequence-alignments (last visited Mar. 1, 2024).

(search results from UniProtKB). Dr. Axelrod found the tetanus toxoid shares "3-13 conserved similar or homologous amino acids with human TRPV1," "3-7 conserved similar or homologous amino acids with human NaV1.7," "3-8 conserved similar or homologous amino acids with human Dorsal Root Ganglion Alpha-7 nicotinic receptor," and "3-8 conserved similar or homologous amino acids with human [CASPR2]." Pet. Ex. 13 at 8; Pet. Ex. 15. He found the diphtheria toxoid shares "3-7 conserved similar or homologous amino acids with human TRPV1," "3-8 conserved similar or homologous amino acids with human NaV1.7," "3-7 conserved similar or homologous amino acids with human NaV1.8," "3-9 conserved similar or homologous amino acids with human Dorsal Root Ganglion Alpha-7 nicotinic receptor," and "3-7 conserved similar or homologous amino acids with human [CASPR2]." Pet. Ex. 13 at 8-9; Pet. Ex. 16.

Dr. Axelrod acknowledged that Ekeruche-Makinde et al.,[33] which studied specific MHC Class I-peptide combinations with respect to activation of CD8+ T-cell receptors, determined the preferred length for peptides to cross-react is eight to 12 amino acids. Pet. Ex. 13 at 7 (citing Pet. Ex. 34). But Hemmer et al. "showed that even small peptides ([three to five] amino acids long) could result in MHC Class II dependent CD4+ T-cell responses." Id. (citing Pet. Ex. 35). Dr. Axelrod noted "[t]hese are the responses that allow immune protection from [t]etanus and [d]iphtheria infection, by reacting to structures of the [t]etanus and [d]iphtheria toxoids, to protect from infection." Id. "If there are similar or homologous structures on self-antigens, then the immune response to the vaccine structures can also react to the self-antigens to cause functional changes and/or damage." Id.

Moreover, Franklid et al.[34] determined that "amino acid similarity, not identity, is a predictive measure of cross-reactivity." Pet. Ex. 13 at 7 (quoting Pet. Ex. 36 at 2). This article is a study of cytotoxic T cell cross-reactivity, and the authors found that "seemingly distinct T cell epitopes, i.e., ones with low sequence identity, are in fact more biochemically similar than expected." Pet. Ex. 36 at 1. The authors found "that if the first amino acid in a cross-reactive pair is identical to the original epitope for which the cross-reactive T-cell clone was first developed, a maximal immune response to the self-antigen would be achieved." Pet. Ex. 13 at 7 (citing Pet. Ex. 36 at 4). Additionally, "they found that the cross-reactive epitopes shared conserved amino acids at the remaining positions, not identical amino acids." Id. (citing Pet. Ex. 36 at 4).

Based on this, Dr. Axelrod opined that "immune responses to the [t]etanus toxoid and the [d]iphtheria [t]oxoid produce immune responses to the neuronal fibers that are involved in [s]mall [f]iber [n]europathy." Pet. Ex. 13 at 9. And in a susceptible host, "these immune

[33] Julia Ekeruche-Makinde et al., Peptide Length Determines the Outcome of TCR/Peptide-MHCI Engagement, 121 Blood 1112 (2013).

[34] Sune Franklid et al., Amino Acid Similarity Accounts for T Cell Cross-Reactivity and for "Holes" in the T Cell Repertoire, 3 PLoS ONE e1831 (2008).

responses to the unmyelinated type C fibers and myelinated type Aδ fibers, with stimulation and/or damage to these neurons, result in [s]mall [f]iber [n]europathy." Id. (citing Pet. Ex. 60).[35]

For further support of molecular mimicry as a causal mechanism for small fiber neuropathy, Dr. Axelrod cited medical literature to posit that small fiber neuropathy is a variant of GBS, and that molecular mimicry has been shown to be a causal mechanism for GBS. Pet. Ex. 53 at 6; Pet. Ex. 13 at 6 (citing Pet. Ex. 61).

Seneviratne and Gunasekera[36] stated "[t]he existence of sensory [GBS] has now been established beyond doubt and it is shown to be a demyelinating neuropathy electrophysiologically." Pet. Ex. 66 at 1. The authors identified six patients with acute small fiber sensory neuropathy who satisfied diagnostic criteria for the pure sensory variant of GBS[37] and demonstrated clinical features compatible with small fiber neuropathy. Id. They postulated that acute small fiber sensory neuropathy could be a subset or variant of GBS. Id. at 1, 3. They suggested that "small sensory [fibers] are a possible target for selective damage by autoantibodies" and recommended "immunological studies to identify the antibodies involved." Id. at 3.

Pan et al.[38] studied cutaneous innervation in patients with GBS to investigate the involvement of small fiber neuropathy in GBS. Pet. Ex. 68 at 1. In the skin of GBS patients, 55% had a reduced number of nerves in both the epidermis and dermis. Id. at 4-5. Pan et al. found that small fiber neuropathy "exist[s] in a significant proportion of GBS patients, and that [epidermal nerve density] values [] correlated with functional disabilities" of GBS. Id. at 1. The authors suggested that GBS should be considered a "global neuropathy" instead of a large fiber neuropathy, which it is traditionally referred to as, because of the involvement of small-diameter nerves. Id. at 1, 8; see also Pet. Ex. 69 at 12 (stating small fibers can be involved in GBS). The authors also suggested that the mechanism for large fiber degeneration in GBS is the same for small-diameter sensory nerves. Pet. Ex. 68 at 10.

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[35] Lori J. Albert & Robert D. Inman, Molecular Mimicry and Autoimmunity, 341 New Eng. J. Med. 2068 (1999).

[36] U. Seneviratne & S. Gunasekera, Acute Small Fibre Sensory Neuropathy: Another Variant of Guillain-Barré Syndrome?, 72 J. Neurology Neurosurgery Psychiatry 540 (2002).

[37] The diagnostic criteria for sensory GBS are "acute onset symmetric sensory loss, progression up to [four] weeks, diminished or absent reflexes, normal muscle power, electrophysiological evidence of demyelination in at least two nerves, monophasic course, no alternative cause for neuropathy, no family history of neuropathy, and increased [cerebrospinal fluid] protein (in some)." Pet. Ex. 66 at 2.

[38] Chun-Liang Pan et al., Cutaneous Innervation in Guillain-Barré Syndrome: Pathology and Clinical Correlations, 126 Brain 386 (2003).

Uncini and Yuki[39] performed a reference search to identify sensory variants of post-infectious GBS and proposed a classification based on the size of the fibers involved and the primary site of damage. Pet. Ex. 67 at 1, 5 fig.1, 6. They identified three different types of sensory GBS, with two types affecting large nerve fibers and the third type, "acute sensory small fiber neuropathy-ganglionopathy," affecting small fibers. Id. at 5 fig.1. Uncini and Yuki observed ten patients whom they described as having acute sensory small fiber neuropathy-ganglionopathy, with symptoms including (1) acute onset of numbness and/or burning and pain in extremities; and (2) distal sensory loss for pain and temperature. Id. at 4. In some of the patients evaluated with the acute sensory small fiber neuropathy-ganglionopathy variant of GBS, skin biopsies showed decreased epidermal nerve fiber densities. Id. The authors found "[t]hese patients may represent cases of post-vaccination GBS involving small fibers." Id. According to Dr. Axelrod, Uncini and Yuki suggested that small fiber neuropathy is a variant of GBS. Pet. Ex. 53 at 6 (citing Pet. Ex. 67 at 1-2, 4, 5 fig.1).

Binder and Baron[40] also reviewed small fiber neuropathy in the context of GBS. Pet. Ex. 70 at 1. The authors found GBS can manifest as a chronic neuropathic pain syndrome and the "finding of small fiber involvement in neuropathic pain syndromes is in line with previous reports of reduced intraepidermal nerve fiber density in skin biopsies of GBS patients." Id.

Yuki et al.[41] described cases of post-infectious GBS with findings consistent with small fiber neuropathy. Pet. Ex. 73 at 1, 4. The case series showed that "an acute immune response can be directed against small fibers and exhibit similarities to [GBS]." Id. at 4.

Min et al.[42] described two cases of sensory GBS following Covid-19 vaccination. Pet. Ex. 71 at 1. The second patient demonstrated positive findings of small fiber neuropathy on skin biopsy, but sensory GBS was considered the most probable diagnosis for both patients. Id. at 3. Finsterer[43] subsequently argued that the second patient in Min et al. had small fiber neuropathy, rather than pure sensory GBS. Pet. Ex. 72 at 1. Finsterer concluded that the second patient in Min et al. "more likely" had distal small fiber neuropathy than small fiber ganglionopathy. Id. They reasoned small fiber neuropathy was a reported side effect of the vaccine and noted the

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[39] Antonino Uncini & Nobuhiro Yuki, Sensory Guillain-Barré Syndrome and Related Disorders: An Attempt at Systemization, 45 Muscle & Nerve 464 (2012).

[40] Andreas Binder & Ralf Baron, Size Matters—Small Fiber Neuropathy in the Guillain-Barré Syndrome, 151 Pain 9 (2010).

[41] Nobuhiro Yuki et al., Acute Painful Autoimmune Neuropathy: A Variant of Guillain-Barré Syndrome, 57 Muscle & Nerve 320 (2018).

[42] Young Gi Min et al., Sensory Guillain-Barre Syndrome Following the ChAdOx1 nCov-19 Vaccine: Report of Two Cases and Review of Literature, 359 J. Neuroimmunology 577691 (2021).

[43] Josef Finsterer, SARS-CoV-2 Vaccinations May Not Only Be Complicated by GBS but Also by Distal Small Fibre Neuropathy, 360 J. Neuroimmunology 577703 (2021).

partial effectiveness to treatment. Id. Dr. Axelrod opined Finsterer "suggest[ed] that [s]mall [f]iber [n]europathy is part of [GBS]." Pet. Ex. 53 at 6.

After explaining that small fiber neuropathy is a variant of GBS, Dr. Axelrod cited literature reporting GBS after vaccination with tetanus and diphtheria component vaccines. Pet. Ex. 53 at 7 (citing Pet. Ex. 75 (noting a possible safety signal for GBS and a meningococcal vaccine containing diphtheria toxoid);[44] Pet. Ex. 76 (finding 10 cases of GBS following tetanus, diphtheria, and acellular pertussis ("Tdap") vaccination);[45] Pet. Ex. 78 (reporting a patient who developed GBS after a pure tetanus toxoid vaccination);[46] Pet. Ex. 79 (reporting two cases of GBS following a meningococcal vaccine containing diphtheria toxoid)).[47]

Dr. Axelrod also noted that the Institute of Medicine ("IOM") in 1994 "found that evidence favored acceptance of a causal relationship between diphtheria and tetanus toxoids and GBS." Pet. Ex. 53 at 7 (quoting Pet. Ex. 74 at 1).[48] However, in 2012, the IOM "did not find credible relationships" between Td and GBS. Id. (citing Pet. Ex. 65 at 63).[49] Dr. Axelrod stated this was because "[t]he number of subjects available was insufficient to make any comment regarding a relationship between Td and [GBS]." Id.

Dr. Axelrod admitted that there are no epidemiological studies showing the Td vaccination results in autoimmune small fiber neuropathy. Pet. Ex. 53 at 5-6. However, he opined the Td vaccine is "incredibly safe" and therefore, the number of afflicted subjects between the vaccinated and unvaccinated in a prospective study is "likely to be incredibly small." Id. And because the required number of subjects in each group must be incredibly large, such "clinical trials or cohort studies are not feasible." Id. Therefore, Dr. Axelrod opined "it is

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[44] Tanya R. Myers et al., Adverse Events Following Quadrivalent Meningococcal Diphtheria Toxoid Conjugate Vaccine (Menactra®) Reported to the Vaccine Adverse Event Reporting System (VAERS), 2005–2016, 38 Vaccine 6291 (2020).

[45] Soju Chang et al., U.S. Postlicensure Safety Surveillance for Adolescent and Adult Tetanus, Diphtheria and Acellular Pertussis Vaccines: 2005–2007, 31 Vaccine 1447 (2013).

[46] Norris Newton, Jr. & Abdorassoi Janati, Guillain-Barré Syndrome After Vaccination with Purified Tetanus Toxoid, 80 S. Med. J. 1053 (1987).

[47] Ctrs. Disease Control & Prevention, Update: Guillain-Barré Syndrome Among Recipients of Menactra® Meningococcal Conjugate Vaccine—United States, October 2005-February 2006, 55 Morbidity & Mortality Wkly. Rep. 364 (2006).

[48] Kathleen R. Stratton et al., Adverse Events Associated with Childhood Vaccines Other Than Pertussis and Rubella, 271 JAMA 1602 (1994).

[49] Inst. of Med., Diphtheria Toxoid-, Tetanus Toxoid-, and Acellular Pertussis-Containing Vaccines, in Adverse Effects of Vaccines: Evidence and Causality 525 (Kathleen Stratton et al. eds., 2012).

not surprising that even simple observational studies have not addressed a relationship of Td vaccination and [s]mall [f]iber [n]europathy." Id. at 6.

For example, the IOM does not address a relationship between small fiber neuropathy and Td vaccination. Pet. Ex. 53 at 6 (citing Pet. Ex. 65). The IOM only addressed small fiber neuropathy in connection to varicella and flu vaccines. Id. (citing Pet. Ex. 65). It found the "epidemiologic evidence insufficient or absent to assess an association between varicella vaccine and small fiber neuropathy."[50] Pet. Ex. 65 at 30.

Dr. Axelrod cited several case reports regarding small fiber neuropathy and vaccination generally, although none involved the Td vaccine. See Pet. Ex. 53 at 6-7. The first, authored by Kafaie et al., described a previously healthy 14-year-old girl who developed small fiber neuropathy after a human papillomavirus ("HPV") vaccine. Pet. Ex. 49 at 1. Kafaie et al. stated "[v]accination has been speculated as a possible etiology of [small fiber neuropathy]" and noted that in an effort to identify possible etiologies of small fiber neuropathy, literature has described vaccine-associated polyneuropathies following flu, Lyme, varicella zoster virus ("VZV"), HPV, and rabies vaccinations. Id. at 1, 4. While various pathological mechanisms have been proposed for vaccine-associated polyneuropathies including immune-mediated hypersensitivity to the solvents/adjuvants, the authors concluded that "the possible association between vaccinations and [small fiber neuropathy] is not well defined." Id. at 4.

Souayah et al.[51] discussed five previously healthy individuals who developed small fiber neuropathy following vaccination for rabies, varicella, and Lyme. Pet. Ex. 50 at 1. A causal association was presumed "based on the temporal relationship between vaccination and symptom onset and the exclusion of more common causes of small fiber neuropathy such as diabetes." Id. at 2. The authors noted that while the pathogenesis of post-vaccination neuropathy is unclear, molecular mimicry is one potential mechanism. Id. at 3.

In summary, Dr. Axelrod opined that the Td vaccine can cause small fiber neuropathy because there is sequence homology between components of the Td vaccine and various small fiber nerve receptors which produces an immune response, and in a susceptible host, the immune response to the unmyelinated type C fibers and myelinated type Aδ fibers causes stimulation and/or damage resulting in small fiber neuropathy. Pet. Ex. 13 at 6-9.

ii. Althen Prong Two

Dr. Axelrod opined Petitioner developed a protective immune response to the Td vaccine. Pet. Ex. 13 at 9. He stated that her immune response to both the tetanus and diphtheria toxoids "represented immune responses to similar conserved, as well as homologous, amino acid sequences found on her unmyelinated type C fibers and myelinated type Aδ fibers, with

[50] Petitioner did not file the portion of the 2012 IOM report on flu vaccines and small fiber neuropathy.

[51] Nizar Souayah et al., Small Fiber Neuropathy Following Vaccination for Rabies, Varicella or Lyme Disease, 27 Vaccine 7322 (2009).

subsequent stimulation and/or damage to these neurons, with resultant [s]mall [f]iber [n]europathy." Id.

However, Dr. Axelrod stated that the vast majority of individuals who receive Td vaccines do not develop small fiber neuropathy. Pet. Ex. 13 at 9. He explained that "the theory of molecular mimicry as a cause of autoimmune disease requires not only homologous/highly conserved[] amino acid sequences between the vaccine and the small nerve fibers, but also a susceptibility of the host to develop such a disease." Pet. Ex. 53 at 5 (citing Pet. Exs. 30, 60-61). Dr. Axelrod posited that Petitioner "must have the susceptibility factors" required to develop autoimmune small fiber neuropathy via molecular mimicry, "including an aberrant immune system," because she did in fact develop small fiber neuropathy and therefore, by definition, "she was susceptible to the disease." Id. at 5, 7; Pet. Ex. 13 at 9. He stated Petitioner "has, at the very least, an aberrant peripheral regulatory network, in addition to the presence of self-reactive B-cells and T-cells as part of her peripheral immune system." Pet. Ex. 53 at 5 (citing Pet. Ex. 63). In addition, he added Petitioner may also have "other predisposing factors that have not yet been identified in subjects with autoimmune [s]mall [f]iber [n]europathy." Id.

Dr. Axelrod admitted he is not a neurologist and thus he left the issue of alternative cause to Dr. Miglis. Pet. Ex. 13 at 9; Pet. Ex. 53 at 1. He noted that small fiber neuropathy may be associated with other conditions. Pet. Ex. 13 at 9-10. However, based on Petitioner's medical records, he eliminated other potential causes including HPV, diabetes, metabolic syndrome, low vitamin B12 levels, abnormal thyroid function tests, hepatitis C infection, and medications Petitioner was taking as alternate causes. Id. at 10-11. Accordingly, Dr. Axelrod opined there was no alternative cause of Petitioner's small fiber neuropathy. Id. at 11. "The only proximate new environmental factor" was the Td vaccine. Id.

iii. **Althen** Prong Three

Dr. Axelrod summarized that the "time frame between the Td injection of June 23, 2019 and the onset of the symptoms (June 26, 2019) that lead to [Petitioner's] diagnosis of small fiber neuropathy[] is consistent with a secondary adaptive immune response to the Td booster that she received." Pet. Ex. 53 at 2.

Petitioner received the Tenivac Td vaccine on June 23, 2019. Pet. Ex. 13 at 1 (citing Pet. Ex. 10 at 68, 166, 169). Dr. Axelrod opined Petitioner developed a "protective immune response" to both the tetanus and diphtheria toxoids contained in Tenivac. Id. at 9. Importantly, Dr. Axelrod noted that Petitioner previously received a Tdap vaccine, which also contains the tetanus and diphtheria toxoids, on September 25, 2013; therefore, she was not naïve to the components. Id. at 9, 14 (citing Pet. Ex. 12 at 3). He opined Petitioner "likely developed a primary adaptive immune response to the tetanus toxoid and diphtheria toxoid that she received on September 25, 2013, with the development of persistent memory cells." Pet. Ex. 53 at 1 (citing Pet. Ex. 32 at 9); see also Pet. Ex. 13 at 9 (opining Petitioner "was primed to develop protective secondary adaptive immune responses to both toxoids"). Therefore, Dr. Axelrod averred "[t]his allowed her to develop a secondary adaptive immune response" to the Tenivac Td vaccine she received on June 23, 2019, resulting in small fiber neuropathy. Pet. Ex. 13 at 14.

Abbas et al. explained that "[e]xposure of the immune system to a foreign antigen enhances its ability to respond to that antigen again." Pet. Ex. 32 at 9. "Responses to second and subsequent exposures to the same antigen" are called "secondary immune responses." Id. "Immunologic memory occurs because each exposure to an antigen generates long-lived memory cells specific for the antigen." Id. After a primary adaptive immune response, "[m]emory cells remain, ready to respond vigorously" if the same antigen returns. Id. at 17.

In his first expert report, Dr. Axelrod stated that Petitioner first experienced symptoms related to her small fiber neuropathy on June 26, 2019, three days after receiving her Td booster vaccine on June 23. Pet. Ex. 53 at 1, 7. While Petitioner also received rabies vaccinations around the same time she received her Td vaccine,[52] Dr. Axelrod opined it was the Td vaccine that caused her small fiber neuropathy. Id. at 7-8. His reasoning was based on the fact that Petitioner was naïve to the rabies vaccine and that the time frame for onset is "most consistent with a secondary adaptive immune response" or a "booster response" to the Td vaccine. Id. at 1, 7; Pet. Ex. 13 at 14.

Dr. Axelrod explained that because there is no evidence Petitioner previously received any rabies vaccinations, she would most likely not develop a secondary immune response to those antigens in June 2019. Pet. Ex. 53 at 1. Instead, it would be expected she would first have a primary adaptive immune response to the rabies vaccines, which can take 10 to 25 days to manifest. Id. at 1, 7-8 (citing Pet. Ex. 81).[53] But he opined the onset of Petitioner's symptoms was too short to be a primary adaptive immune response as would be expected from the rabies vaccines. Id. at 1-2, 4, 7-8. "Therefore, it is unlikely that Petitioner's condition, which developed three days following these exposures, ha[d] anything to do with the rabies [vaccinations] or rabies treatments." Id. at 8. "However, as [Petitioner] had prior exposure to both the tetanus toxoid and the diphtheria toxoids, a secondary adaptive immune response to re-exposure to the tetanus toxoid and diphtheria toxoid (the booster received on June 23, 2019) would be likely." Id. at 2.

Citing Abbas et al., Dr. Axelrod explained a secondary adaptive immune response can peak two to three days following a booster immunization. Pet. Ex. 13 at 11; Pet. Ex. 53 at 2 (citing Pet. Ex. 32 at 8 fig.1.2). Similarly, Miller et al.[54] "studied the secondary adaptive immune response using a tetanus toxoid probe. They found that the secondary adaptive immune response began to rise between [two] and [four] days following the booster injection." Pet. Ex.

[52] Petitioner received rabies immunoglobulin and the Imovax rabies vaccine on June 23, 2019. Pet. Ex. 10 at 68, 173-74. Petitioner received her first dose of the Rabavert rabies vaccine on June 26, 2019. Id. at 68.

[53] Thomas J. Lawley et al., A Prospective Clinical and Immunological Analysis of Patients with Serum Sickness, 311 New Eng. J. Med. 1407 (1984).

[54] John J. Miller et al., The Speed of the Secondary Immune Response to Tetanus Toxoid with a Review of War Reports and Observations on Simultaneous Injection of Toxoid and Antitoxin, 3 Pediatrics 64 (1949).

13 at 12; Pet. Ex. 53 at 3 (citing Pet. Ex. 40 at 8 fig.4). And Wyatt and Levy[55] found that "full activation of the immune system, including memory T cells, should occur during the first couple of days following a booster immunization." Pet. Ex. 13 at 13; Pet. Ex. 53 at 4 (citing Pet. Ex. 41 at 19 fig.12).

Therefore, Dr. Axelrod opined "the time interval between the Tenivac injection and the development of [Petitioner's] [s]mall [f]iber [n]europathy of about [three] days is consistent with a secondary adaptive immune response to the Tenivac injection. The time interval is too short for a primary adaptive immune response, which would be expected from the rabies treatments." Pet. Ex. 53 at 4.

2. Petitioner's Expert, Dr. Mitchell Gordon Miglis[56]

a. Background and Qualifications

Dr. Miglis is a board-certified neurologist. Pet. Ex. 44 at 1. He received his M.D. from the University of Florida College of Medicine and subsequently completed an internship in internal medicine at Washington Hospital Center/Georgetown University, a neurology residency at New York University Hospitals, and a fellowship in Clinical Neurophysiology/Autonomic Disorders at Beth Israel Deaconess Medical Center of Harvard Medical School. Id. During his time in practice, Dr. Miglis estimated that he has managed "over three hundred unique patients with small fiber neuropathy." Pet. Ex. 43 at 2. Dr. Miglis is currently a faculty member in the Neurology Department at Stanford University during which he supervises the autonomic testing of patients in the autonomic laboratory at Stanford University and interprets the results to aid in the proper diagnosis of autonomic disorders, including small fiber neuropathy. Id. He also teaches within the scope of autonomic neurology on a regular basis to medical students, residents, fellows, and other physicians. Id. Dr. Miglis has authored or co-authored numerous publications and serves on the editorial board for a peer-reviewed autonomic journal. Id.; Pet. Ex. 44 at 8-14.

b. Opinion

Dr. Miglis opined that Petitioner's "diagnosis of small fiber neuropathy is related to the Tenivac vaccination that she received." Pet. Ex. 43 at 7; Pet. Ex. 54 at 5.

i. Althen Prong One

Dr. Miglis reviewed Dr. Axelrod's expert reports and opined that the mechanism proposed by Dr. Axelrod, molecular mimicry "given the homology between amino acid sequences of the tetanus and diphtheria toxoid present in the Tenivac Td vaccine and various small nerve fiber receptors such as TRPV1, NaV1.7 and NaV1.8," is sound and reliable. Pet. Ex.

[55] Asia Wyatt & Doron Levy, Modeling the Effect of Memory in the Adaptive Immune Response, 82 Bull. Mathematical Biology 124 (2020).

[56] Petitioner filed two expert reports from Dr. Miglis. Pet. Exs. 43, 54.

43 at 4 (citing Pet. Ex. 13 at 9). Accordingly, Dr. Miglis "agree[d] with the details of [Dr. Axelrod's expert] report in its entirety." Id.

He described small fiber neuropathy and noted that because "the small nerve fibers are long, thin, and minimally protected by the myelin sheath that surrounds large nerve fibers, they are especially vulnerable to inflammatory injury, as seen in autoimmune disease." Pet. Ex. 43 at 3. He added that autoimmune disease is often triggered by molecular mimicry. Pet. Ex. 54 at 2.

Dr. Miglis also recognized that "sequence homology by itself does not demonstrate causation." Pet. Ex. 54 at 3. He explained that "sequence homology provides the foundation for molecular mimicry to occur. Thus, in a predisposed individual, autoimmune disease simply needs an environmental trigger and host tissue with the same or similar sequence homology for cross-reactivity to occur." Id. He acknowledged that little is known about genetic or environmental susceptibility factors that predispose individuals to autoimmune diseases resulting in neurological complications. Id. at 2. Dr. Miglis added that this is true for not only small fiber neuropathy and GBS, but also diseases of the central nervous system. Id.

Like Dr. Axelrod, Dr. Miglis cited case reports of small fiber neuropathy after vaccination to show an association and to further support an autoimmune mechanism. Pet. Ex. 43 at 3-4 (citing Pet. Ex. 48;[57] Pet. Ex. 49; Pet. Ex. 50; Pet. Ex. 51).[58] He added that "up to 1982, 14 cases of peripheral neuropathy after tetanus toxoid injection were reported in publications worldwide." Id. at 4 (quoting Pet. Ex. 48 at 2).

As to epidemiologic evidence, Dr. Miglis agreed with Dr. Axelrod that "performing a prospective study evaluating this association would not be feasible due to the rarity of vaccine injury and the extremely large sample sizes needed to demonstrate significant results." Pet. Ex. 54 at 1. Dr. Miglis opined "establishing a causal relationship between vaccination and autoimmune disease is especially difficult because vaccines induce disease in a limited number of genetically susceptible individuals, thus limiting the power of epidemiological studies to detect such a signal." Id. This is especially true with vaccine-induced injuries that are rare, difficult to diagnose, and "may not be reflected in epidemiological studies using non-specific ICD codes."[59] Id.

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[57] John D. Holden, Benefits and Risks of Childhood Immunisations in Developing Countries, 294 Brit. Med. J. 1329 (1987).

[58] Waqar Waheed et al., Post COVID-19 Vaccine Small Fiber Neuropathy, 64 Muscle & Nerve E1 (2021).

[59] ICD-9 codes (the International Classification of Diseases, Ninth Revision) "is the official system of assigning codes to diagnoses and procedures associated with hospital utilization in the United States." International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), Ctrs. for Disease Control & Prevention: Nat'l Ctr. for Health Stats., https://www.cdc.gov/nchs/icd/icd9cm.htm (last visited Mar. 19, 2024).

Here, Dr. Miglis explained that small fiber neuropathy can be difficult to diagnose as the symptoms are non-specific. Pet. Ex. 54 at 1. Moreover, there is no ICD-9 code for small fiber neuropathy. Id. at 2. "The ICD-9 code most often used, 356.9, is that of 'unspecified idiopathic peripheral neuropathy,' and does not discriminate between large or small fiber disease." Id. Therefore, Dr. Miglis opined that Yih et al.,[60] which Dr. Leist relied on, "was not designed to detect cases of [small fiber neuropathy] after Tdap vaccination, as they relied on ICD-9 codes for outcome measures." Id. (citing Resp. Ex. K).

ii. Althen Prong Two

Given that Petitioner had no pre-existing symptoms of small fiber neuropathy and developed a non-length-dependent small fiber neuropathy after her Tenivac Td vaccination, "in the absence of a more plausible explanation," Dr. Miglis opined that Petitioner's "diagnosis of small fiber neuropathy is related to the Tenivac vaccination that she received." Pet. Ex. 43 at 7; Pet. Ex. 54 at 5.

Dr. Miglis disagreed that the alternative etiologies proposed by Dr. Leist would be "more likely triggers than the Td vaccination [Petitioner] received three days prior to symptom onset." Pet. Ex. 54 at 4.

First, Dr. Miglis acknowledged that while Petitioner had a documented history of vitamin B12 deficiency, her B12 levels were normal at the time of her small fiber neuropathy diagnosis on September 13, 2019. Pet. Ex. 54 at 4 (citing Pet. Ex. 8 at 34).

Second, Dr. Miglis explained that "alcoholic neuropathy only occurs in very heavy drinkers." Pet. Ex. 54 at 4 (citing Pet. Ex. 55). While Petitioner was drinking alcohol the night prior to receiving her Td vaccine, "there are no reports of consistent heavy drinking or concerns of alcoholism in her record." Id. (citing Pet. Ex. 8 at 13).

Third, while Dr. Miglis admitted glucose intolerance can cause small fiber neuropathy, and Petitioner had several mildly elevated glucose levels, Dr. Miglis explained that small fiber neuropathy "due to glucose intolerance is typically subacute and progressive in nature, as opposed to [Petitioner's] acute presentation, which is more consistent with an immune-mediated process." Pet. Ex. 54 at 4. Further, Dr. Miglis explained that small fiber neuropathy due to glucose intolerance "is most commonly length-dependent (affecting distal areas such as the feet before proximal areas such as the thighs or hands), and [Petitioner's] [small fiber neuropathy] was non-length dependent, which is also more commonly seen in immune-mediated etiologies." Id.

Instead, Dr. Miglis opined Petitioner's "decline from her pre-vaccine state of functioning is striking, and there are many features to suggest an autoimmune mechanism." Pet. Ex. 43 at 7; Pet. Ex. 54 at 5. As such, he opined there is no other plausible explanation and that there is a

[60] W. Katherine Yih et al., An Assessment of the Safety of Adolescent and Adult Tetanus–Diphtheria–Acellular Pertussis (Tdap) Vaccine, Using Active Surveillance for Adverse Events in the Vaccine Safety Datalink, 27 Vaccine 4257 (2009). This is also cited as Pet. Ex. 59.

logical sequence of cause and effect between the Td vaccine and her development of small fiber neuropathy. Pet. Ex. 54 at 5.

iii. Althen Prong Three

Dr. Miglis agreed with Dr. Axelrod that the onset of Petitioner's symptoms was approximately three days from her Td vaccination and that this timeframe is consistent with a secondary adaptive immune response. Pet. Ex. 54 at 3, 5; Pet. Ex. 43 at 7. He stated this was particularly reasonable for an autoimmune response with a vaccine to which Petitioner was not naïve. Pet. Ex. 43 at 7; Pet. Ex. 54 at 5.

He further agreed that "the timeframe of manifestation of symptoms after the initial rabies vaccination is too rapid to posit causation." Pet. Ex. 54 at 3. He explained Petitioner "was naïve to this vaccination, and thus would have had a primary immune response to this antigen—a process taking longer to occur." Id. Therefore, Dr. Miglis posited Petitioner's "autoimmune disease [was] far more likely to be due to the Td vaccination." Id.

3. Respondent's Expert, Dr. Thomas P. Leist[61]

a. Background and Qualifications

Dr. Leist is a board-certified neurologist that specializes in neuroimmunology. Resp. Ex. A at 1. He received his Ph.D. in biochemistry at the University of Zurich in Switzerland and received his M.D. from University of Miami in Florida, where he also completed an internship in internal medicine. Resp. Ex. B at 1. Thereafter he completed a residency in neurology at Cornell Medical Center/Sloan Kettering Memorial Cancer Center in New York. Id. He also was a fellow in the Department of Microbiology and Immunology at the University of California, Los Angeles. Id. As a member of the neurology faculty at Thomas Jefferson University, Dr. Leist participates in classroom instruction and clinical education of medical students, as well as teaching and supervising residents and directing the fellowship program in clinical neuroimmunology. Resp. Ex. A at 1. Dr. Leist is "regularly involved in the care of patients with neuroimmunological conditions including multiple sclerosis, neuromyelitis optica spectrum disorder, transverse myelitis, [GBS], chronic inflammatory demyelinating polyneuropathy[,] and other autoimmune conditions of the nervous system." Id. He has authored or co-authored numerous publications in neuroimmunology. Resp. Ex. B at 6-17.

b. Opinion

Dr. Leist opined Petitioner did not experience an adverse event following the Td vaccination on June 23, 2019. Resp. Ex. A at 9; Resp. Ex. L at 4. He reasoned the Td vaccine is not known to cause small fiber neuropathy, that a time interval of three days is too short to infer vaccine causation, and that Petitioner had other conditions that are associated with small fiber neuropathy. Resp. Ex. A at 9; Resp. Ex. L at 4.

[61] Respondent filed two expert reports from Dr. Leist. Resp. Exs. A, L.

i. Althen Prong One

Dr. Leist interpreted Dr. Axelrod's theory as representing (1) "that Td is a known cause of immune mediated small fiber neuropathy," (2) "that the mere presence of limited sequence homologies between administered and endogenous proteins [] suffices as evidence that a pathobiologically relevant cross reactive immune response can occur," and (3) that Petitioner had "identified 'predisposing factors' which rendered her vulnerable to the allegedly [Td] induced small fiber neuropathy." Resp. Ex. A at 5. Dr. Leist had objections to each of these propositions.

First, Dr. Leist opined that "there is no literature that supports a causal association between the Tdap vaccine [and] small fiber neuropathy." Resp. Ex. A at 6 (citing Resp. Ex. E at 1).[62] "Absent reputable evidence," Dr. Leist opined that "Dr. Axelrod's claim of a Td/Tdap vaccine inducing an immune response against cutaneous small fibers is speculative." Id.

While Dr. Leist opined that "GBS is distinct from small fiber neuropathy and vice versa," he acknowledged that the vaccine-induced mechanisms of injury for both conditions would "share common mechanistic elements." Resp. Ex. A at 6. As such, he cited the 2012 IOM report which "reviewed mechanic considerations regarding an association between [GBS], an acute inflammatory disease of the peripheral nerves, and diphtheria toxoid, tetanus toxoid, or acellular pertussis-containing vaccines." Id. Dr. Leist explained that while the IOM wrote that "'[a]utoantibodies, complement activation, immune complexes, T cells, and molecular mimicry may contribute to the symptoms of GBS[,]' the literature reviewed for the report 'did not provide evidence linking these mechanisms to diphtheria toxoid–, tetanus toxoid–, or acellular pertussis–containing vaccine[s].'" Id. (quoting Pet. Ex. 65 at 64). Thus, Dr. Leist concurred with the 2012 IOM's assessment. Id. Dr. Leist did not address the fact that the IOM previously reached a different outcome. See Pet. Ex. 74 at 1.

Dr. Leist cited literature to support his position that tetanus and diphtheria components do not cause small fiber neuropathy. Resp. Ex. A at 6-7. He cited Yih et al., which studied the safety of the Tdap vaccine compared to the Td vaccine. Resp. Ex. K at 1. They studied 660,000 individuals who received the Tdap vaccine and used previous data on 890,000 individuals who received the Td vaccine as comparison. Id. at 1-2. The authors only selected encephalopathy-encephalitis-meningitis, paralytic syndromes, seizures, cranial nerve disorders, and GBS (based on their respective ICD-9 codes) as outcomes to focus on in the study. Id. at 1, 2 tbl.1. The authors found no evidence of an association between the Tdap vaccine and the predefined adverse events, confirming that the Tdap vaccine does not increase the risk of those predefined events any more than the Td vaccine. Id. at 5. However, the authors did not study small fiber neuropathy as an adverse event. See id. at 1, 2 tbl.1.

[62] Scott A. Halperin et al. Randomized Controlled Trial of the Safety and Immunogenicity of Revaccination with Tetanus-Diphtheria-Acellular Pertussis Vaccine (Tdap) in Adults 10 Years After a Previous Dose, 8 J. Pediatric Infectious Diseases Soc'y 105 (2019). This is also cited as Pet. Ex. 58.

Daley et al.[63] studied more than 200,000 children who received a diphtheria, tetanus, acellular pertussis and inactivated polio virus combined vaccine ("DTaP–IPV"). Resp. Ex. D at 1. Ninety-seven percent of the DTaP-IPV recipients also received other vaccines that same day, typically measles-mumps-rubella ("MMR") and varicella vaccines. Id. Again using ICD-9 codes, the study focused on eight potential adverse events: meningitis/encephalitis, seizures, stroke, GBS, Stevens-Johnson syndrome, anaphylaxis, serious allergic reactions other than anaphylaxis, and serious local reactions. Id. at 1, 2 tbl.1. The authors found "no evidence of increased risk for any of the pre-specified adverse events monitored" when compared to the historical incidence rates; however, they suggested continued surveillance for rare events such as GBS. Id. at 1, 5. But like Yih et al., Daley et al. did not study small fiber neuropathy as an adverse event. See id. at 1, 2 tbl.1. Thus, Dr. Leist did not cite any study that specifically evaluated small fiber neuropathy as an adverse event of vaccination.

Second, Dr. Leist appeared to posit that the mere presence of limited sequence homology is insufficient for a relevant cross reactive immune response to occur. Resp. Ex. A at 5. For support, he cited literature which noted that "short sequence homologies "exist, and the vast majority of these are not associated with biologically relevant autoimmune phenomena or actual human disease." Resp. Ex. L at 2 (citing Resp. Ex. J at 2);[64] see also Resp. Ex. A at 7. Dr. Leist agreed that Dr. Axelrod identified sequence homologies between tetanus and/or diphtheria toxoid and peptides allegedly relevant to small fiber neuropathy. Resp. Ex. L at 2. But he asserted that neither Dr. Axelrod nor Dr. Miglis "provide[d] information that links tetanus and/or [diphtheria] toxoid to induction of T cells specific for antigens of small nerve fibers or B cells secreting pathologically relevant auto-antibodies that cross reacts with small nerve fibers." Id.

Dr. Leist cited Chan et al.[65] to identify the relevant autoantibodies in small fiber neuropathy. Resp. Ex. L at 2 (citing Resp. Ex. P). "Chan et al. tested sera from patients diagnosed with idiopathic small fiber neuropathy against more than 1,600 immune related antigens." Id. (citing Resp. Ex. P at 1). The authors "detected nine autoantibodies against the antigens they tested." Id. (citing Resp. Ex. P at 1, 7 fig.4). Dr. Leist opined that Chan et al. showed that "it is testable whether tetanus and/or diphtheria toxoid contain vaccines induce autoantibodies against small fiber neurons." Id. According to Dr. Leist, Chan et al. supported (1) the finding that "autoantibodies can be detected in select patients with small fiber neuropathy, but it is not known whether these autoantibodies occur in response to nerve injury, or precede it, and it is not known whether or not they cause injury to the small nerve cells or are just an epiphenomenon;" and (2) the "hypothesis of whether tetanus and/or pertussis containing

[63] Matthew F. Daley et al., Safety of Diphtheria, Tetanus, Acellular Pertussis and Inactivated Polio Virus (DTaP–IPV) Vaccine, 32 Vaccine 3019 (2014).

[64] Inst. of Med., Evaluating Biological Mechanisms of Adverse Events, in Adverse Effects of Vaccines: Evidence and Causality, supra note 49, at 57.

[65] Amanda C.Y. Chan et al., Novel Autoantibodies in Idiopathic Small Fiber Neuropathy, 91 Annals Neurology 66 (2022).

vaccines induce autoantibodies reactive with constituents of small fiber neurons can be tested[66] but there are no reports showing that this occurs." Id. Additionally, Dr. Leist opined that "Chan et al. does not report autoantibodies against the proteins identified by Dr. Axelrod based on sequence homologies." Id.

Lastly, while Dr. Axelrod proposed that sequence homology can result in injury to individuals with predisposing factors, Dr. Leist agreed that "[m]arkers of susceptibility that . . . render an individual vulnerable to [Td] vaccine induced small fiber neuropathy are not known." Resp. Ex. A at 7. He explained there is "no literature that informs on characteristics that, if present, put the individual at risk for small fiber neuropathy in response to a Td/Tdap vaccine," and that Dr. Axelrod did not provided evidence of or a method of determining such predisposed factors. Id.

ii. Althen Prong Two

Dr. Leist opined "there are no findings or measures in [Petitioner's] case that show a clinically apparent immune response following administration of Td vaccine" on June 23, 2019. Resp. Ex. L at 1. He reasoned that if the Td vaccine "had initiated a significant early secondary immune response to Td . . . there would likely have been signs of inflammation at the site of inoculation, the area of greatest concentration of vaccine components." Id. However, he did not believe this was documented in the records. Id. Dr. Leist did not cite any medical literature or other evidence to support this opinion.

Next, Dr. Leist discussed "possible alternate causes of small fiber neuropathy." Resp. Ex. A at 5. First, he noted that in addition to the Td vaccine, Petitioner also received four doses of rabies vaccines around the same time. Id. Dr. Leist opined that Petitioner's experts did not show what "pathologic considerations" led them to eliminate the rabies vaccines as a cause of Petitioner's immune-mediated small fiber neuropathy. Id. at 5, 7. Despite Dr. Leist criticizing Petitioner's experts for opining sequence homology is sufficient to prove molecular mimicry as a mechanism of disease, he noted that there are sequence homologies between rabies virus and endogenous protein sequences. Id. at 7 (citing Pet. Ex. 28). He also faulted Petitioner's experts for failing to "explain why sequence homologies between rabies virus, rabies vaccines contain[ing] inactivated rabies virus, and endogenous proteins would be less relevant to [Petitioner's] theory of causation than those [] listed for tetanus and diphtheria toxin." Id.

Second, Dr. Leist averred Petitioner had "preexisting conditions known to cause small fiber neuropathy," including elevated blood glucose levels and vitamin B12 deficiency as documented in the medical records. Resp. Ex. L at 4 (citing Resp. Ex. C;[67] Resp. Ex. M).[68]

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[66] Petitioner was not tested for such antibodies.

[67] B.T.A. de Greef et al., Associated Condition in Small Fiber Neuropathy – A Large Cohort Study and Review of the Literature, 25 Eur. J. Neurology 348 (2018).

[68] Hafize Nalan Güneş et al., The Histopathological Evaluation of Small Fiber Neuropathy in Patients with Vitamin B12 Deficiency, 118 Acta Neurologica Belgica 405 (2018).

While de Greef et al. did not identify associated conditions in 53% of their patients with small fiber neuropathy, they noted that autoimmune diseases, sodium channel gene mutations, diabetes mellitus including glucose intolerance, and vitamin B12 deficiencies were the most prevalent findings. Id. (citing Resp. Ex. C at 1). Dr. Leist noted that Petitioner was not tested to see if she carried the sodium channel gene mutations known to cause small fiber neuropathy. Id.

As for Petitioner's B12 deficiency, although Petitioner's B12 levels were normal at the time of her small fiber neuropathy diagnosis, Dr. Leist noted Petitioner was also taking B12 supplements at that time. Resp. Ex. L at 4. Dr. Leist seemed to posit that small fiber neuropathy associated with B12 deficiency is not reversed with B12 supplementation. Id. He cited Güneş et al. for the proposition that "vitamin B12 deficiency causes symptomatic as well as asymptomatic small fiber loss like diabetes mellitus." Id. (quoting Resp. Ex. M at 1).

iii. Althen Prong Three

Dr. Leist opined that "[i]n absence of a known relationship between the Tdap vaccine and small fiber neuropathy, it is not possible to know what the biologically plausible time interval for this complication to occur would be." Resp. Ex. A at 8. But even if there was an established relationship, Dr. Leist opined Petitioner's symptoms consistent with peripheral neuropathy occurred outside the biologically plausible timeframe for a vaccine-induced process. Id. at 7.

Relying on contemporary records, Dr. Leist wrote that Petitioner "developed symptoms suggestive of small fiber neuropathy no later than June 26, 2019." Resp. Ex. A at 8.

Petitioner received her Td vaccination on June 23, 2019, and Dr. Leist noted that on June 28, 2019, Petitioner endorsed a two-day history of left leg pain and numbness. Resp. Ex. A at 8. Review of symptoms included "fatigue and night sweats, sinus congestion, abdominal pain, light-headedness, arthralgia, muscle stiffness, light-headedness, numbness or shooting pain in hands, arms, legs or feet, excessive daytime sleepiness, and excessive worrying." Id. (quoting Pet. Ex. 10 at 117). Dr. Leist pointed out that the "contemporary records do not stipulate whether the listed symptoms had been present for more than two days." Id.

Dr. Leist criticized Dr. Axelrod's use of Abbas et al. to show that a secondary adaptive immune response may peak by two to three days. Resp. Ex. L at 2. He explained the "unit value of the x-axis of Figure 1.2 of Abbas [et al.] is 'weeks' and antibody titers to the recall antigen appear to peak around days [seven] to 10 not [two to three] days as Dr. Axelrod note[d]." Id. (citing Pet. Ex. 32 at 8 fig.1.2). Moreover, he added that neither Abbas et al. nor Miller et al. "inform whether tetanus or toxoid containing vaccines induce an immune response against small fiber neurons, under what conditions this might occur, or when clinical symptoms would be expected following a booster dose of the vaccine." Id. (citing Pet. Ex. 53 at 2-3; Pet. Ex. 32 at 8 fig.1.2; Pet. Ex. 40 at 8 fig.4).

Instead, Dr. Leist cited Hahn et al.[69] and Mausberg et al.,[70] which "studied aspects of the kinetics of onset of [experimental autoimmune neuritis ("EAN")] following adoptive transfer of T cells reactive with peripheral nerve components." Resp. Ex. L at 3 (citing Resp. Exs. N-O). According to Dr. Leist, this "experimental model can serve to inform on the minimal time interval between administration of a preformed immune response against peripheral nerves and onset of clinical disease." Id. Hahn et al. found that "recipients became sick [four to eight] days post transfer and the degree of disability correlated directly with the dose of T cells administered." Resp. Ex. N at 1. Mausberg et al. found "[c]linical signs of neuritis were observed only after day [three] to [four] days post-adoptive transfer of neuritogenic T cells." Resp. Ex. O at 4. Dr. Leist summarized that "Hahn et al. and Mausberg et al. found that even when preformed and activated autoreactive T cells were transferred into [] susceptible hosts[,] clinical signs of neuritis, i.e. autoimmune neuropathy, [were] observed not earlier than starting on day [four] after adoptive transfer of autoreactive T cells." Resp. Ex. L at 3.

Applying the observations of Hahn et al. and Mausberg et al. here, Dr. Leist opined "the time interval of at most [three] days between administration of the Td-booster is outside of the biologically plausible time interval for a putative preformed, autoreactive immune response stimulated by a recall antigen (Td vaccine) to cause small fiber neuropathy." Resp. Ex. L at 3. Moreover, he opined Dr. Axelrod's theory of causation "requires the existence of immune cells cross-reactive with small fiber neurons" prior to receipt of Petitioner's Td vaccine. Id. But according to Dr. Leist, Dr. Axelrod did "not provide information as to how a Td booster could activate a putative dormant autoreactive T cells and cause small fiber neuropathy within [three] days following vaccination when the overt clinical disease can only be observed on day[] [four] and after following administration of activated autoreactive T cells." Id. at 3-4.

In conclusion, Dr. Leist averred Petitioner's "alleged symptoms of small fiber neuropathy occurred less than three days following administration of the [Td] vaccine . . . which is a shorter onset than would generally be accepted for immune mediated peripheral neuropathy in the Vaccine Program." Resp. Ex. A at 8.

III. DISCUSSION

A. Standards for Adjudication

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty

[69] A.F. Hahn et al. Adoptive Transfer of Experimental Allergic Neuritis in the Immune Suppressed Host, 86 Acta Neuropathologica 596 (1993).

[70] Anne K. Mausberg et al., Trapped in the Epineurium: Early Entry into the Endoneurium is Restricted to Neuritogenic T Cells in Experimental Autoimmune Neuritis, 15 J. Neuroinflammation 217 (2018).

and generosity.'" Rooks v. Sec'y of Health & Hum. Servs., 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. Moberly v. Sec'y of Health & Hum. Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Hum. Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Petitioner need not make a specific type of evidentiary showing, i.e., "epidemiologic studies, rechallenge, the presence of pathological markers or genetic predisposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect." Capizzano v. Sec'y of Health & Hum. Servs., 440 F.3d 1317, 1325 (Fed. Cir. 2006). Instead, Petitioner may satisfy her burden by presenting circumstantial evidence and reliable medical opinions. Id. at 1325-26.

In particular, a petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface v. Sec'y of Health & Hum. Servs., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also Pafford v. Sec'y of Health & Hum. Servs., 451 F.3d 1352, 1355 (Fed. Cir. 2006). The received vaccine, however, need not be the predominant cause of the injury. Shyface, 165 F.3d at 1351. A petitioner who satisfies this burden is entitled to compensation unless Respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B). However, if a petitioner fails to establish a prima facie case, the burden does not shift. Bradley v. Sec'y of Health & Hum. Servs., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

"Regardless of whether the burden ever shifts to the [R]espondent, the special master may consider the evidence presented by the [R]espondent in determining whether the [P]etitioner has established a prima facie case." Flores v. Sec'y of Health & Hum. Servs., 115 Fed. Cl. 157, 162-63 (2014); see also Stone v. Sec'y of Health & Hum. Servs., 676 F.3d 1373, 1379 (Fed. Cir. 2012) ("[E]vidence of other possible sources of injury can be relevant not only to the 'factors unrelated' defense, but also to whether a prima facie showing has been made that the vaccine was a substantial factor in causing the injury in question."); de Bazan v. Sec'y of Health & Hum. Servs., 539 F.3d 1347, 1353 (Fed. Cir. 2008) ("The government, like any defendant, is permitted to offer evidence to demonstrate the inadequacy of the [P]etitioner's evidence on a requisite element of the [P]etitioner's case-in-chief."); Pafford, 451 F.3d at 1358-59 ("[T]he presence of multiple potential causative agents makes it difficult to attribute 'but for' causation to the vaccination. . . . [T]he Special Master properly introduced the presence of the other unrelated contemporaneous events as just as likely to have been the triggering event as the vaccinations.").

B. Causation

To receive compensation through the Program, Petitioner must prove either (1) that she suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that she suffered an injury that was actually caused by a vaccination. See §§ 11(c)(1), 13(a)(1)(A); Capizzano, 440 F.3d at 1319-20. Petitioner must

show that the vaccine was "not only a but-for cause of the injury but also a substantial factor in bringing about the injury." Moberly, 592 F.3d at 1321 (quoting Shyface, 165 F.3d at 1352-53).

Because Petitioner does not allege she suffered a Table Injury, she must prove a vaccine she received actually caused her injury. To do so, Petitioner must establish, by preponderant evidence: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." Althen, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. Petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." Knudsen v. Sec'y of Health & Hum. Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether Petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The special master must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in Petitioner's favor when the evidence weighs in her favor. See Moberly, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor).

Testimony that merely expresses the possibility—not the probability—is insufficient, by itself, to substantiate a claim that such an injury occurred. See Waterman v. Sec'y of Health & Hum. Servs., 123 Fed. Cl. 564, 573-74 (2015) (denying Petitioner's motion for review and noting that a possible causal link was not sufficient to meet the preponderance standard). The Federal Circuit has made clear that the mere possibility of a link between a vaccination and a petitioner's injury is not sufficient to satisfy the preponderance standard. Moberly, 592 F.3d at 1322 (emphasizing that "proof of a 'plausible' or 'possible' causal link between the vaccine and the injury" does not equate to proof of causation by a preponderance of the evidence); Boatmon v. Sec'y of Health & Hum. Servs., 941 F.3d 1351, 1359-60 (Fed. Cir. 2019). While certainty is by no means required, a possible mechanism does not rise to the level of preponderance. Moberly, 592 F.3d at 1322; see also de Bazan, 539 F.3d at 1351.

IV. ANALYSIS

A. Althen Prong One

Under Althen prong one, Petitioner must set forth a medical theory explaining how the received vaccine could have caused the sustained injury. Andreu v. Sec'y of Health & Hum. Servs., 569 F.3d 1367, 1375 (Fed. Cir. 2009); Pafford, 451 F.3d at 1355-56. Petitioner's theory of causation need not be medically or scientifically certain, but it must be informed by a "sound

and reliable" medical or scientific explanation. Boatmon, 941 F.3d at 1359; see also Knudsen, 35 F.3d at 548; Veryzer v. Sec'y of Health & Hum. Servs., 98 Fed. Cl. 214, 257 (2011) (noting that special masters are bound by both § 13(b)(1) and Vaccine Rule 8(b)(1) to consider only evidence that is both "relevant" and "reliable"). If Petitioner relies upon a medical opinion to support her theory, the basis for the opinion and the reliability of that basis must be considered in the determination of how much weight to afford the offered opinion. See Broekelschen v. Sec'y of Health & Hum. Servs., 618 F.3d 1339, 1347 (Fed. Cir. 2010) ("The special master's decision often times is based on the credibility of the experts and the relative persuasiveness of their competing theories."); Perreira v. Sec'y of Health & Hum. Servs., 33 F.3d 1375, 1377 n.6 (Fed. Cir. 1994) (stating that an "expert opinion is no better than the soundness of the reasons supporting it" (citing Fehrs v. United States, 620 F.2d 255, 265 (Ct. Cl. 1980))).

The undersigned finds Petitioner has set forth a sound and reliable medical theory, molecular mimicry, to explain how the Td vaccine can cause small fiber neuropathy. The medical literature shows persuasive evidence of the similarity between GBS and small fiber neuropathy, that molecular mimicry is an appropriate causal mechanism of GBS, and therefore by analogy, is sound and reliable here. Further, the undersigned finds, independently of the relation to GBS, support for Dr. Axelrod's opinion that the Td vaccine can cause small fiber neuropathy via molecular mimicry.

First, the medical literature and opinions of Dr. Axelrod provide evidence of the similarities between small fiber neuropathy and GBS. See, e.g., Pet. Ex 73 at 4 (suggesting that "an acute autoimmune response can be directed against small fibers and exhibit similarities to [GBS]"); Pet. Ex. 68 at 8 (finding diminished epidermal innervation in some GBS patients, suggesting that "small-[fiber] sensory neuropathy is also an important manifestation of GBS, and that GBS should be considered a global neuropathy instead of a pure large-[fiber] neuropathy"); Pet. Ex. 67 at 1 (recognizing cases in which patients diagnosed with acute sensory neuropathy may in fact have GBS); Pet. Ex. 66 at 1 (postulating small fiber neuropathy may be a subtype of sensory GBS); Pet. Ex. 61 at 1 (indicating "autoimmune disorders share common immunopathogenic mechanisms").

While Dr. Leist opines that GBS and small fiber neuropathy are distinct from each other, he admits that the vaccine-induced mechanisms of injury for both conditions would "share common mechanistic elements," and accordingly cites literature involving GBS. Resp. Ex. A at 6.

Other special masters have concluded that small fiber neuropathy can be seen as a variant of GBS. In Fiske, the special master found preponderant evidence that small fiber neuropathy is a variant of GBS where the petitioner presented much of the same literature filed here. Fiske v. Sec'y of Health & Hum. Servs., No. 17-1378V, 2023 WL 8352761, at *26-28 (Fed. Cl. Spec. Mstr. Nov. 13, 2023); see also Swaiss v. Sec'y of Health & Hum. Servs., No. 15-286V, 2019 WL 6520791, at *13 (Fed. Cl. Spec. Mstr. Nov. 4, 2019) (finding the petitioner had "adequately supported the existence of an immune-mediated small fiber neuropathy, which may be referred to as a small fiber GBS variant").

In other cases, special masters have found that small fiber neuropathy is sufficiently similar to GBS such that the mechanisms are analogous. See, e.g., Doe v. Sec'y of Health & Hum. Servs., No. [redacted]V, 2007 WL 3120297, at *7-8 (Fed. Cl. Spec. Mstr. Oct. 18, 2007) (finding the petitioner had preponderantly shown that the flu vaccine caused her serum sickness and small fiber neuropathy, accepting the petitioner's evidence that GBS and small fiber neuropathy were sufficiently similar to be analogous for purposes of her theory of causation); Quirino v. Sec'y of Health & Hum. Servs., No. 17-989V, 2023 WL 9229145, at *19-21 (Fed. Cl. Spec. Mstr. Dec. 18, 2023) (finding the petitioner's small fiber neuropathy was consistent with GBS); Jones v. Sec'y of Health & Hum. Servs., No. 15-1239V, 2018 WL 7139212, at *13-14 (Fed. Cl. Spec. Mstr. Dec. 21, 2018) (finding the petitioner's argument that GBS and small fiber neuropathy were sufficiently similar to be persuasive).

Although, the decisions of other special masters are not binding on the undersigned, she agrees generally with the reasoning of her colleagues in this Ruling. See Boatmon, 941 F.3d at 1358; Hanlon v. Sec'y of Health & Hum. Servs., 40 Fed. Cl. 625, 630 (1998), aff'd, 191 F.3d 1344 (Fed. Cir. 1999).

Here, while the undesigned does not find that small fiber neuropathy is a variant of GBS, she does find the pathophysiology of small fiber neuropathy analogous to GBS, and that molecular mimicry is an appropriate causal mechanism of GBS.

The experts agree, and many of the medical articles filed, establish that GBS is known to be an autoimmune condition, and that molecular mimicry is a likely causal mechanism. For example, Rojas et al. provides a comprehensive analysis of the relevant immunological theories of causation in GBS, specifically molecular mimicry. Mausberg et al. states that molecular mimicry is the leading pathophysiological factor in GBS. Cusick et al. and Fourneau et al. also sufficiently describe molecular mimicry in autoimmune diseases such as GBS and small fiber neuropathy.

Further, literature supports an association between vaccines containing tetanus and diphtheria toxoids and GBS. See, e.g., Pet. Ex. 76 (finding 10 cases of GBS following Tdap vaccination); Pet. Ex. 78 (reporting a patient who developed GBS after a pure tetanus toxoid vaccination).

Moreover, in the Vaccine Program, molecular mimicry has been accepted as a sound and reliable theory in many demyelinating conditions, including GBS, and those conditions that cause damage to unmyelinated small neurons, which is what occurs in small fiber neuropathy. See, e.g., Barone v. Sec'y of Health & Hum. Servs., No. 11-707V, 2014 WL 6834557, at *8-9 (Fed. Cl. Spec. Mstr. Nov. 12, 2014) (noting molecular mimicry "has been accepted in other Program cases as a reliable medical explanation for how various autoimmune conditions could develop after the receipt of different kinds of vaccinations"); Conte v. Sec'y of Health & Hum. Servs., No. 17-403V, 2020 WL 5743696, at *57 (Fed. Cl. Spec. Mstr. July 27, 2020) (noting the theory of molecular mimicry in a GBS case is "well-established and well-settled in the Vaccine Program"); E.M. v. Sec'y of Health & Hum. Servs., No. 14-753V, 2021 WL 3477837, at *36-39 (Fed. Cl. Spec. Mstr. July 9, 2021) (finding molecular mimicry a sound and reliable theory for how the flu vaccine can cause small fiber neuropathy).

The undersigned also finds that there is scientific support for Dr. Axelrod's theory that illustrates how molecular mimicry could cause small fiber neuropathy without relying on the similarity with GBS. First, Petitioner provided preponderant evidence that small fiber neuropathy can result from autoimmunity. Both Dr. Axelrod and Dr. Miglis cite medical literature to opine small fiber neuropathy can be autoimmune and that Petitioner here has the autoimmune type. See, e.g., Pet. Ex. 69 at 12 (indicating small fiber neuropathy is immune-mediated); Pet. Ex. 22 at 2 tbl.1 (suggesting small fiber neuropathy is sometimes immune-mediated); Pet. Ex. 46 at 3, 7 (identifying autoimmunity as a cause for small fiber neuropathy). And Cusick et al. and Fourneau et al. describe molecular mimicry as a trigger for autoimmune diseases.

Next, Dr. Axelrod identified components of the Td vaccine that can initiate the development of antibodies, cross-react with small fiber nerve receptors, and trigger an autoimmune response. Consistent with the medical literature filed herein, Dr. Axelrod explains that TRPV1, CASPR2, sodium channels (NaV1.7 and NaV1.8), and nicotine receptors "form parts of the unmyelinated type C fibers and myelinated type Aδ fibers" that are stimulated and/or damaged in small fiber neuropathy. Pet. Ex. 13 at 9. Dr. Axelrod conducted a UniProtKB search to determine there is sequence homology between the human peptides associated in small fiber neuropathy and tetanus and/or diphtheria toxoids, present in the Td vaccine at issue. And Hemmer et al. provides that small peptide sequences can result in T-cell responses.

Dr. Leist does not dispute the results of Dr. Axelrod's UniProt KB search. Instead, he opines that evidence of homology is not enough evidence of molecular mimicry to induce autoimmune disease. Dr. Leist argues Petitioner's experts "do not provide information that links tetanus and/or pertussis toxoid to induction of T cells specific for antigens of small nerve fibers or B cells secreting pathologically relevant auto-antibodies that cross reacts with small nerve fibers." Resp. Ex. L at 2.

But although demonstrated here, Petitioner need not make a specific type of evidentiary showing or require identification of homology to prove that molecular mimicry is a sound and reliable theory by preponderant evidence. Given the state of current scientific knowledge, there is no way that a petitioner could satisfy such a requirement. Further, requiring proof of specific homology or proof of identical protein sequences between the Td vaccine and the peripheral nervous system to prove causation would require scientific certainty, which is a bar too high. See Knudsen, 35 F.3d at 549 (explaining that "to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program").

Dr. Leist relies on GBS literature to show that in 2012, the IOM did not find a causal relationship between the tetanus toxoid or diphtheria toxoid and GBS. However, Dr. Leist does not address the fact that the IOM previously reached the opposite conclusion. Regardless, the lack of epidemiological evidence is not dispositive. It is difficult to use epidemiology to determine whether a vaccine is implicated in causation. Because while adverse reactions like this do not appear in the newest epidemiological evidence cited by Dr. Leist, it may be that events are too rare to be captured, as suggested by Petitioner's experts. Moreover, "[r]equiring

epidemiologic studies . . . or general acceptance in the scientific or medical communities . . . impermissibly raises a claimant's burden under the Vaccine Act and hinders the system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." Andreu, 569 F.3d at 1378 (quoting Capizzano, 440 F.3d at 132-26); see also Althen, 418 F.3d at 1280 (noting that "close calls" are resolved in Petitioner's favor). The undersigned does not find the lack of epidemiological literature to be determinative in this regard.

Thus, Dr. Axelrod produced literature to show that small fiber neuropathy involves TRPV1, CASPR2, sodium channels, and nicotine receptors, and evidence of homology with the tetanus and diphtheria toxoids. He has shown that vaccines containing tetanus and diphtheria toxoids can induce an autoimmune response leading not only to GBS, but to stimulation and/or damage to unmyelinated type C fibers and myelinated type Aδ fibers resulting in small fiber neuropathy. And he establishes the Td vaccine at issue here, contains the components that cross-react with the neuronal fibers. For each aspect of his theory, Petitioner has provided scientific support through medical literature.

Lastly, vaccine causation has been found in several cases of immune-mediated small fiber neuropathy. See, e.g., Fiske, 2023 WL 8352761, at *28-30 (finding the flu vaccine caused small fiber neuropathy via molecular mimicry); E.M., 2021 WL 3477837, at *36-39 (finding the petitioner developed small fiber neuropathy following a recall response to the flu vaccine with a theory of molecular mimicry); Doe, 2007 WL 3120297, at *6-7 (finding an immune response after the flu vaccine caused small fiber neuropathy); Swaiss, 2019 WL 6520791, at *24-27 (finding small fiber neuropathy is a variant of GBS, and that the Tdap vaccine can and did cause the petitioner's condition via molecular mimicry); Jones, 2018 WL 7139212, at *13-14 (finding the petitioner succeeded in establishing vaccinations could cause small fiber neuropathy with a theory of molecular mimicry but denying entitlement based on Althen prongs two and three). The undersigned generally agrees with the reasoning of her colleagues in these cases as to Althen prong one.

Other special masters denied entitlement but not based on Althen prong one. McGill v. Sec'y of Health & Hum. Servs., No. 15-1485V, 2023 WL 3813524 (Fed. Cl. Spec. Mstr. May 11, 2023) (denying compensation where onset was only eight hours); Todd v. Sec'y of Health & Hum. Servs., No. 15-860V, 2020 WL 727973 at *21 (Fed. Cl. Spec. Mstr. Jan. 8, 2020) (determining the petitioner did not suffer from small fiber neuropathy); Fantini v. Sec'y of Health & Hum. Servs., No 15-1332V, 2022 WL 1760730, at *19-21 (Fed. Cl. Spec. Mstr. May 2, 2022) (finding the petitioner did not preponderantly establish small fiber neuropathy as the likely injury); Lapierre v. Sec'y of Health & Hum. Servs., No. 17-227V, 2019 WL 6490730, at *18-19 (Fed. Cl. Spec. Mstr. Oct. 18, 2019) (determining the record did not support a diagnosis of small fiber neuropathy).

For these reasons, the undersigned finds that Petitioner has provided preponderant evidence of a sound and reliable causal theory, satisfying Althen prong one.

B. Althen Prong Two[71]

Under Althen prong two, Petitioner must prove by a preponderance of the evidence that there is a "logical sequence of cause and effect showing that the vaccination was the reason for the injury." Capizzano, 440 F.3d at 1324 (quoting Althen, 418 F.3d at 1278). "Petitioner must show that the vaccine was the 'but for' cause of the harm . . . or in other words, that the vaccine was the 'reason for the injury.'" Pafford, 451 F.3d at 1356 (internal citations omitted).

In evaluating whether this prong is satisfied, the opinions and views of the vaccinee's treating physicians are entitled to some weight. Andreu, 569 F.3d at 1367; Capizzano, 440 F.3d at 1326 ("[M]edical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" (quoting Althen, 418 F.3d at 1280)). Medical records are generally viewed as trustworthy evidence, since they are created contemporaneously with the treatment of the vaccinee. Cucuras v. Sec'y of Health & Hum. Servs., 993 F.2d 1525, 1528 (Fed. Cir. 1993). While the medical records and opinions of treating physicians must be considered, they are not binding on the special master. § 13(b)(1)(B) (specifically stating that the "diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court").

The undersigned finds that Petitioner provided preponderant evidence of a logical sequence of cause and effect showing that her vaccination was the cause of her small fiber neuropathy. First, Petitioner's clinical course is consistent with the medical literature and case reports of small fiber neuropathy following vaccination.

Petitioner received the Td vaccine on June 23, 2019. The first medical record documenting Petitioner's symptoms was on June 28, 2019, when Petitioner presented to her physician with leg pain and numbness for the past two days. By August 2019, Petitioner's symptoms worsened and she had difficulty walking. Physical examination revealed "decreased sensation to her left lower leg." Pet. Ex. 10 at 68. The diagnosis was numbness lower extremity. Nurse Jaorasdr "discussed [Petitioner's] decreased sensation in her left leg possibly being from nerve damage secondary to vaccinations." Id. Petitioner further reported left leg weakness and was diagnosed with neuropathy of the left peroneal nerve and left leg numbness and weakness. Petitioner had subsequent testing and eventually presented to neurologist Dr. Saperstein whose assessment was that Petitioner had "sensory symptoms and multifocal distributions. This came on surely after tetanus and rabies injections. Possible that there was some immune response to these." Pet. Ex. 8 at 14. A skin biopsy on September 27, 2019 showed "[a]bnormal nerve fiber density at the distal site . . . consistent with a length-dependent neuropathy affecting the small nerve fibers." Pet. Ex. 8 at 39. Dr. Saperstein's assessment was that "this [was] likely the result of an autoimmune reaction to the vaccinations." Id. Dr. Saperstein also submitted a letter stating Petitioner's small fiber neuropathy was "likely the result of an autoimmune reaction to a vaccination." Pet. Ex. 57 at 1

[71] Both Dr. Axelrod and Dr. Leist appear to agree that Petitioner had a predisposition or susceptibility that played a role in causation, although the individual markers of such are not known. See Pet. Ex. 13 at 6, 9; Resp. Ex. A at 7.

As evidenced in this summary of the evidence, some of Petitioner's healthcare providers attributed her condition to an immune response from vaccination. Generally, treating physician statements are typically "favored" as treating physicians "are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury.'" Capizzano, 440 F.3d at 1326 (quoting Althen, 418 F.3d at 1280). However, no treating physician's views bind the special master, per se; rather, their views are carefully considered and evaluated. § 13(b)(1); Snyder, 88 Fed. Cl. at 746 n.67. "As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases." Welch v. Sec'y of Health & Hum. Servs., No. 18-494V, 2019 WL 3494360, at *8 (Fed. Cl. Spec. Mstr. July 2, 2019). The undersigned finds Dr. Saperstein's statements on an autoimmune cause of her small fiber neuropathy persuasive as they align with Petitioner's expert reports.

Further, the undersigned finds there is no alternative cause to Petitioner's autoimmune small fiber neuropathy. Respondent's expert Dr. Leist offers opinions as to alternate causes for Petitioner's small fiber neuropathy, namely her vitamin B12 deficiency. Dr. Leist opines that while Petitioner was taking B12 supplements, "vitamin B12 deficiency causes symptomatic as well as asymptomatic small fiber loss." Resp. Ex. L at 4 (quoting Resp. Ex. M at 1). However, Petitioner's B12 levels were normal at the time of her small fiber neuropathy diagnosis and Dr. Leist acknowledges that.

Moreover, Dr. Leist fails to state his opinion as to an alternative cause to a reasonable degree of probability. He discusses possible alternate causes of small fiber neuropathy based on Petitioner's past medical history, including a controlled vitamin B12 deficiency, and her rabies vaccinations, but he does not express the opinion, more likely than not, that either the B12 deficiency or the rabies vaccine was the cause of Petitioner's small fiber neuropathy. Accordingly, the undersigned finds that Dr. Leist's opinions do not carry sufficient weight to support alternative causation.

Thus, the undersigned finds that Petitioner provided preponderant evidence of a logical sequence of cause and effect, satisfying Althen prong two.

C. Althen Prong Three

Althen prong three requires Petitioner to establish a "proximate temporal relationship" between the vaccination and the injury alleged. Althen, 418 F.3d at 1281. That phrase has been defined as a "medically acceptable temporal relationship." Id. A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352. The explanation for what is a medically acceptable time frame must also coincide with the theory of how the relevant vaccine can cause the injury alleged (under Althen Prong One). Id.; see also Koehn v. Sec'y of Health & Hum. Servs., 773 F.3d 1239, 1243-44 (Fed. Cir. 2014); Shapiro, 101 Fed. Cl. at 542.

At the outset, the undersigned notes that it is difficult to determine the date of onset here. Petitioner's experts opine that Petitioner's onset of symptoms began on June 26, 2019, three days post-vaccination. Dr. Leist opines Petitioner's symptoms began "less than" three days after her vaccination and "no later than" June 26, 2019. Resp. Ex. A at 8.

Petitioner received her Td vaccination on June 23, 2019. The earliest-in-time medical record documenting Petitioner's symptoms was on June 28, 2019, when Petitioner presented to her physician with leg pain and numbness for the past two days. This places onset on June 26, three days after her vaccination. The subsequent records documenting onset are inconsistent.

For example, at Petitioner's next appointment, on August 9, 2019, Nurse Jaorasdr noted that Petitioner's left leg numbness "started approximately [six] weeks ago," which would be June 28, 2019. Pet. Ex. 10 at 64. And on August 23, 2019, Petitioner saw Dr. Sobel who wrote that Petitioner noticed left leg numbness two days after her June 23 ED visit, which would be June 25, 2019.

The neurologists' records are also inconsistent as to date of onset. On September 6, 2019, at Petitioner's initial neurology consultation, Dr. Pawar wrote that Petitioner started having symptoms a "[f]ew days later" after her vaccination, which the undersigned interprets to be three days, or June 26, 2019.[72] Pet. Ex. 7 at 3. On September 13, 2019, Dr. Saperstein noted Petitioner's symptoms began two days after her June 23 ED visit and vaccination, which would be June 25, 2019.[73]

Further, Petitioner's statement from 2020 is inconsistent with the medical records. Petitioner wrote that on June 25, 2019, her "leg kept losing feeling" and by June 28, she noticed her symptoms getting worse. Pet. Ex. 1 at ¶¶ 4-5. However, this is inconsistent with the earliest-in-time medical record on June 28, documenting leg pain and numbness for two days (starting on June 26). Moreover, on June 25, 2019, Petitioner had an appointment with Nurse Gruwell and did not report any symptoms such as leg pain or numbness. See Pet. Ex. 10 at 146-150.

As the Federal Circuit has stated, although "it [is] not erroneous to give greater weight to contemporaneous medical records than to later, contradictory testimony," it is also not the case that "medical records are presumptively accurate and complete. Nor did we state that when a person is ill, he reports all his problems to his doctor, who then faithfully records everything he is told." Kirby v. Sec'y of Health & Hum. Servs., 997 F.3d 1378, 1382-83 (Fed. Cir. 2022) (citing Cucuras, 993 F.2d 1525). The undersigned does not rely solely on the lack of symptoms reported on June 25, 2019. Rather, the absence of reported symptoms on June 25 in conjunction with Petitioner endorsing symptoms for two days on June 28, and Dr. Leist's agreement that

[72] See Jewell v. Sec'y of Health & Hum. Servs., No. 16-0670V, 2017 WL 7259139, at *3 (Fed. Cl. Spec. Mstr. Aug. 4, 2017) (finding "a few days" after vaccination to be within 72 hours); Taylor v. Sec'y of Health & Hum. Servs., No. 16-1403V, 2020 WL 6706078, at *16 (Fed. Cl. Spec. Mstr. Oct. 20, 2020) (finding "few" to mean two or three days).

[73] Dr. Saperstein also wrote in his statement on March 6, 2023, that Petitioner's small fiber neuropathy "started two days after receiving" the Td and rabies vaccines. Pet. Ex. 57 at 1.

onset of Petitioner's symptoms occurred no later than June 26, 2019, all weigh heavily in the undersigned's decision to find onset was June 26, 2019, or three days after vaccination. See Hargrove ex rel. A.F.M. v. Sec'y of Health & Hum. Servs., No. 17-233V, 2023 WL 8071917, at *30 (Fed. Cl. Spec. Mstr. Oct. 27, 2023) (finding the earlier-in-time records more reliable where subsequent records were inconsistent).

Having determined onset to be no more than three days, the next question is whether there is "preponderant proof that the onset of symptoms occurred within a time frame for which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation-in-fact." de Bazan, 539 F.3d at 1352.

Dr. Axelrod and Dr. Miglis opine the medically acceptable timeframe for molecular mimicry here is two to three days. Importantly, they opine Petitioner developed a secondary adaptive immune response rather than a primary adaptive immune response. Petitioner's experts reason that because Petitioner previously received a Tdap vaccine in 2013, she was not naïve to the tetanus and diphtheria components. Specifically, Dr. Axelrod explains Petitioner "likely developed a primary adaptive immune response to the tetanus toxoid and diphtheria toxoid that she received on September 25, 2013, with the development of persistent memory cells." Pet. Ex. 53 at 1. This allowed her to be "primed to develop" a "secondary adaptive immune response" to the Td vaccine on June 23, 2019, resulting in small fiber neuropathy. Pet. Ex. 13 at 9, 14. Dr. Leist does not dispute that Petitioner received a Tdap vaccine in 2013 or that she likely developed persistent memory cells.

Dr. Axelrod relies on Abbas et al. for the proposition that a secondary adaptive immune response can peak two to three days following a booster immunization.[74] Abbas et al. describes how after primary exposure to an antigen and a primary immune response, if memory cells remain, then exposure to the same antigen can "respond vigorously" in a secondary adaptive immune response. Pet. Ex. 32 at 17, 8 fig.1.2. Wyatt and Levy state that memory cells drive the secondary response, resulting in an immune response "that is faster and of greater magnitude" than a primary response.[75] Pet. Ex. 41 at 4.

While Dr. Leist argues that Figure 1.2 in Abbas et al. is measured in weeks not days, none of the studies cited by Dr. Leist support his position that "the time interval of at most [three] days between administration of the Td-booster is outside of the biologically plausible time interval for a putative preformed, autoreactive immune response stimulated by a recall antigen (Td vaccine) to cause small fiber neuropathy." Resp. Ex. L at 3. Dr. Leist's reliance on Hahn et al. is insufficient. Hahn et al. studied EAN in animals. Given the difference in

[74] Dr. Axelrod also cites Miller et al. for the proposition that the immune system can activate two to four days following immunization. However, it is unclear whether the information is applicable given the age of this study. Moreover, there are many variables in this study that cannot be confirmed.

[75] For a thorough explanation of the immune system, the adaptive immune response, and the differences between primary and secondary response, see Pet. Ex. 32; Pet. Ex. 41.

methodology between the study and the facts and circumstances here, it is not clear that the onset timeframe in the study (of at least four days) can be extrapolated to this case.

Likewise, Mausberg et al. is also an animal study which found clinical signs of neuritis observed within three to four days after transfer of neuritogenic cells. They found it took longer, at least four days, before T cells were found in the endoneurium, or the connective tissue around the myelin sheath of myelinated nerve fibers in the peripheral nervous system. Mausberg et al. studied the sciatic nerves in rats. Thus, it is not clear that these timeframes are applicable in smaller nonmyelinated nerves affected in small fiber neuropathy.

In all, the undersigned finds an onset of two to three days for molecular mimicry is supported by the medical literature as an appropriate temporal association. Among the series of post-vaccination small fiber neuropathy cases reported by Souayah et al., two had onset occurring within 24 hours of vaccination. Pet. Ex. 50 at 3. Min et al. described a patient with a three-day onset of sensory GBS following vaccination.

Additionally, a maximum onset of three days is consistent with other small fiber neuropathy cases. In Quirino, the special master found 48 hours to be an appropriate temporal relationship between the petitioner's Hepatitis B and Tdap vaccinations and the development of small fiber neuropathy with a theory of molecular mimicry. Quirino, 2023 WL 9229145, at *23-24. In E.M. the special master found four to six hours an appropriate timeframe for a recall (secondary) response for flu vaccine-induced small fiber neuropathy via molecular mimicry. E.M., 2021 WL 3477837, at *42-44. But see McGill, 2023 WL 3813524, at *34-35 (finding eight to nine hours too rapid for vaccine-induced small fiber neuropathy via molecular mimicry even with a recall (secondary) response theory).

Moreover, in comparing the pathophysiology of small fiber neuropathy to GBS, this temporal association is also consistent with the onset period of three to 42 days as set forth in the Vaccine Injury Table for GBS following flu vaccination. 42 C.F.R. § 100.3(a)(XIV)(D).

Based on this evidence, the undersigned finds that three days is a medically appropriate timeframe for a secondary immune response to the Td vaccine. While two to three days is an early onset, the Federal Circuit has cautioned against "setting a hard and fast deadline . . . between vaccination and [] onset." Paluck v. Sec'y of Health & Hum. Servs., 786 F.3d 1373, 1383-84 (Fed. Cir. 2015) (finding "[t]he special master [] erred in setting a hard and fast deadline" for onset and noting that the medical literature filed in the case "do not purport to establish any definitive timeframe for onset of clinical symptoms"). Therefore, it reasonable and appropriate to find that the onset of Petitioner's small fiber neuropathy is within the appropriate timeframe given the mechanism of molecular mimicry.

Therefore, the undersigned finds the temporal association is appropriate given the mechanism of injury and Petitioner has satisfied the third Althen prong.

D. Alternative Causation

Because the undersigned concludes that Petitioner established a prima facie case, Petitioner is entitled to compensation unless Respondent can put forth preponderant evidence "that Petitioner's injury was in fact caused by factors unrelated to the vaccine." Whitecotton v. Sec'y of Health & Hum. Servs., 17 F.3d 374, 376 (Fed. Cir. 1994), rev'd on other grounds sub nom., Shalala v. Whitecotton, 514 U.S. 268 (1995); see also Walther v. Sec'y of Health & Hum. Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007). As discussed above in the Althen prong two analysis, the undersigned found Respondent failed to establish evidence to show that Petitioner's small fiber neuropathy was caused by a source other than vaccination. Thus, Respondent did not prove by a preponderance of evidence that Petitioner's injury is "due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

V. CONCLUSION

For the reasons discussed above, the undersigned finds that Petitioner has established by preponderant evidence that her Td vaccine caused her small fiber neuropathy. Therefore, Petitioner is entitled to compensation. A separate damages order will issue.

IT IS SO ORDERED.

s/Nora Beth Dorsey
Nora Beth Dorsey
Special Master